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The combination of FLT3 inhibition and hypomethylation confers synergistic anti-leukemic activity on FLT3/ITD positive AML cell lines and primary cells

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Effective treatment regimens for elderly FLT3/ITD+ AML patients represent a significant unmet need in the field. Recent data on the effects of the FLT3 tyrosine kinase inhibitor quizartinib on FLT3/ITD+ AML showed promising clinical activity, including in elderly patients. Hypomethylating agents such as decitabine and azacitidine demonstrated clinical benefit in AML, are well tolerated, and are associated with minimal increases in FLT3 ligand, which can represent a potential resistance mechanism to FLT3 inhibitors. In addition, both FLT3 inhibition and hypomethylation therapy are associated with the induction of terminal differentiation of myeloid blasts. Consequently, there is a strong theoretical rationale for combining FLT3 inhibition and hypomethylation for FLT3/ITD+ AML, particularly in the elderly. We therefore utilized proliferation and apoptosis assays to study the antileukemic effects of decitabine, azacitidine and quizartinib, either as single agents or in combination, on AML cell lines and primary cells derived from newly diagnosed and relapsed AML patients. Our studies indicate that i) stroma blunts the effect of all treatments, ii) azacitidine exerts more cytotoxic effects than decitabine, at least from the standpoint of inducing growth inhibition or apoptosis, iii) combined treatment results in synergistic antileukemic effects that are more pronounced in the presence of stroma as compared to the absence of stroma, and iv) a trend towards greater cytotoxicity can be observed when the drugs are administered simultaneously, rather than in a sequential mode. Combined treatment using FLT3 inhibition and hypomethylation therefore may provide a novel therapeutic approach for FLT3/ITD+ AML, particularly for older patients.

Biography

Heiko Konig received his MD and Doctorate degrees from the medical schools at the Ludwig Maximilians University Munich and the Philipps University Marburg/Germany, respectively. He has a long time interest in targeting deregulated signaling pathways and drug resistance in myeloid leukemias and has published several papers in journals such as Blood, Cancer Research and Leukemia. Following his medical training in Germany he joined Dr. Ravi Bhatia's lab at City of Hope, Duarte/CA, as a Postdoctoral fellow from 2005-2008. From 2008-2011, he underwent residency training in Internal Medicine at the St. Louis University Hospital in St. Louis/MO. He is currently an Assistant Professor of Medicine at the Indiana University Melvin & Bren Simon Cancer Center in Indianapolis, starting in July 2014. He is board certified in Internal Medicine and Medical Oncology.

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