Hematology-2013
OMICS Group Conferences
Accelerating Scientific Discovery
International Conference on
Hematology & Blood Disorders
September 23-25, 2013 Raleigh, USA

AML: Current concepts, recent advances and future directions

Prithviraj Bose
Virginia Commonwealth University, USA

Abstract

Despite major advances in recent years in elucidating the biology of AML, it remains a devastating disease. Approximately 12,000 new cases of AML are diagnosed in the US each year, and two-thirds of young adults and 90% of older adults with AML still die of their disease. The median age at diagnosis of AML has been steadily increasing, and is now around 72 years. The elderly and those in whom AML arises secondary to previous chemotherapy or an antecedent hematologic disorder have a particularly grim prognosis. Finally, the outlook for patients with relapsed or refractory AML is especially gloomy, with relatively few obtaining a durable second complete remission with conventional salvage chemotherapy regimens and going on to successful allogeneic stem cell transplantation (SCT).

Cytogenetic factors have traditionally been key determinants of prognosis in AML. Molecular sub-classification of the classic "good", "intermediate" and "poor" risk categories have yielded both better insights into the heterogeneity within these groups and opportunities for targeted therapy. Thus, *FLT3* mutations, present in ~25-35% cases of AML, are strongly associated with cytogenetically normal AML, high relapse rates and a poor prognosis. Small-molecule inhibitors of the FLT3 tyrosine kinase are at the forefront of targeted therapy of AML, with quizartinib (AC220) appearing to be the most promising to date, although mutations conferring resistance to this drug have already been described. Similarly, mutations in *KIT* may distinguish a subgroup with a less favorable prognosis within the traditionally "good-risk" group of patients with core binding factor (CBF) AML, and could perhaps be targeted by small molecules such as dasatinib.

Testing for mutations in *FLT3, NPM1* and *CEBPA* is now well-established in routine clinical practice and may inform therapeutic decision-making, inasmuch as the mutational status of these genes is often used to decide which patients should or should not undergo allogeneic SCT in first complete remission. However, mutations in many other genes (e.g., *DNMT3A*) continue to be described, along with their prognostic relevance. The Cancer Genome Atlas project has provided several important insights into AML biology in this regard.

Besides FLT3 and KIT inhibitors, a plethora of novel agents, both alone and in combination, are being investigated in the treatment of AML. These include HDAC, proteasome and cyclin-dependent kinase (CDK) inhibitors, checkpoint abrogators, BH3-mimetics, aurora, Pim and polo-like kinase inhibitors, and inhibitors of neddylation. So far, results of clinical trials of some of these agents have been modest, while others are currently in preclinical stages of testing. Other strategies using conventional cytotoxic agents include the delivery of daunorubicin and cytarabine in a fixed molar ratio to AML cells. A particularly promising combination involves "timed sequential therapy" with the CDK inhibitor flavopiridol (alvocidib), followed by cytarabine and mitoxantrone. A randomized phase II trial comparing this regimen ("FLAM") to conventional "7+3" in newly diagnosed adults ≤ 70 with non-CBF AML has just completed accrual.After decades of little progress in the therapeutic arena in AML, it is an exciting time in the field that promises some real breakthroughs that may bring renewed hope to our patients.

Biography

Dr. Bose obtained his medical degree from the University of Calcutta in Kolkata, India before pursuing postgraduate training in the US. After completing his residency in internal medicine at Henry Ford Hospital in Detroit, MI and a fellowship in hematology/oncology at the University of Oklahoma, he joined the faculty at Virginia Commonwealth University (VCU), where he is currently an Assistant Professor. Dr. Bose's research at the NCI-designated VCU Massey Cancer Center focuses on the myeloid malignancies in general, and AML in particular, where he attempts to translate laboratory-based concepts involving rational combinations of targeted agents into early phase clinical trials. In the clinic, Dr. Bose takes care of patients with the whole gamut of hematologic malignancies. Dr. Bose has authored multiple articles and chapters that have appeared in leading journals and books, and serves as the editor-in-chief of *Drug Target Insights.* He has also served as a peer-reviewer for numerous journals. Earlier this year, Dr. Bose was granted permanent residence in the United States in the "outstanding researcher" category.