Biological and molecular effects of selective inhibitor of ‘Aurora Kinase B’ (Barasertib) on a human promyelocytic leukemia cell line

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Introduction: The Aurora (Aur) family of serine/threonine kinases has been implicated in the survival and proliferation of both hematologic and solid malignancies. Overexpression of Aurora kinase B has been shown in a variety of human cancers including leukemia and lymphoma. In the quest for novel anti-cancer agents, several inhibitors of aurora kinases such as AZD1152 (Barasertib) have been introduced. Barasertib has shown preliminary activity in clinical studies of patients with acute myeloid leukemia (AML). The pharmacokinetic and metabolic profiles of Barasertib were characterized in Phase I/II study. The objective of this study was to evaluate the molecular and biological effects of AZD1152 on NB-4 Cell line as an acute promyelocytic leukaemia (APL).

Methods: NB4 Cells treated with various concentrations of AZD1152 and incubated in culture for several days. Transcriptional alteration of genes involved in apoptosis, viability, metabolic activity, morphological changes, nuclear shape variations, cell cycle distribution and apoptosis of inhibitor-treated NB4 cells were assessed using Real Time PCR, trypan blue dye exclusion, MTT, wright-giemsa staining, DAPI staining and flowcytometry assays, respectively.

Results: It was shown that metabolic activity and viability of NB4 cells reduced and in contrast, cell size, G2/M arrest, polyploidy giant cells formation and apoptotic population increased in a concentration and/or time-dependent manner after exposure to AZD1152. In addition, it was observed an expressive enhancement in mRNA levels of p73, Bax, Puma and Bcl-2 coupled with a significant increase in Bax/Bcl-2 molecular ratio.

Conclusion: Our data indicate that AZD1152 induces p73, which in turn up-regulates p53 target genes and orchestrates apoptosis in a p53-independent manner. This inhibitor may be beneficial to refractory APL or resistance to chemotherapy and also further investigation is required to prove this effect.

Biography

Farhad Zaker is working as a Professor of Hematology and Assistant Head of Department of Haematology and Blood Banking at Iran University Medical Sciences. He completed PhD in Haematology in 1997 from University of Wales, College of Medicine, Cardiff-UK. His research interests include haematology, immunohaematology, cell culture & molecular medicine.

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