

Synergistic effects of selective inhibitors targeting the PI3K/AKT/mTOR pathway and NUP214-ABL1 fusion protein in human acute lymphoblastic leukemia

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Acute lymphoblastic leukemia (ALL) is a neoplasm of precursor cells committed to the B-cell and T-cell lineages involving bone marrow and blood, with a rapid onset and frequent chemotherapy resistance and refractory relapses (1). Philadelphia chromosome-positive (Ph+) ALL accounts for 25–30% of adult ALL and its incidence increases with age in adults >40 years old. Irrespective of age, the ABL1 fusion genes, among which BCR-ABL1 is the most commonly found, are markers of very poor prognosis. Amplification of the NUP214-ABL1 oncogene can be detected only in patients with T-ALL (2). The PI3K/Akt/mTOR signaling pathway is activated in many solid cancers and in leukemias and plays a crucial role in tumorigenesis. Furthermore, the presence of RTKs (Receptor Tyrosine Kinases) by ABL1 fusion proteins may result in activation of the PI3K/Akt/mTOR axis. T cell malignancies bearing the ABL1 fusion genes are sensitive to many cytotoxic agents, but up to date complete remissions have not been found. In this work we analyzed the effects of three BCR-ABL1 tyrosine kinase inhibitors (TKIs), alone and in combination with a panel of selective PI3K/Akt/mTOR inhibitors, on two NUP214-ABL1 positive T-ALL cell lines, ALL-SIL and PEER that also displayed Akt hyperactivation. Cells were sensitive to anti BCR-ABL1 TKIs Imatinib, Nilotinib and GZD824, that specifically targeted the ABL1 fusion protein, but not the PI3K/Akt/mTOR axis as deduced by a readout of drug efficacy, four drugs against the PI3K/Akt/mTOR cascade, GSK690693, NVP-BGT226 (BGT226), ZSTK474 and Torin-2, showed a relevant cytotoxic efficacy on T-leukemic cells, without affecting the NUP214-ABL1 kinase and related pathway. Dephosphorylation of pAkt and pS6 showed the cytotoxicity of the compounds. Either single or combined administration of drugs against the different targets displayed inhibition of cellular viability which was associated with a concentration-dependent induction of apoptosis, cell cycle arrest in G0/G1 phase and autophagy, having the combined treatments a significant synergistic cytotoxic effect. Co-targeting NUP214-ABL1 fusion gene and PI3K/Akt/mTOR signaling pathway could represent a new and effective pharmacological strategy to improve the outcome in NUP214-ABL1 positive T-ALL.

References

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Keywords

BCR-ABL1; PI3K/Akt/mTOR signalling; T-acute lymphoblastic leukemia; targeted therapies; autophagy.