IJAE
Vol. 120, n. 1 (Supplement): 73, 2015
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Three hits are superior than one: multiple Akt inhibition as a new therapeutic strategy in T-ALL

Simona Ultimo[1], Carolina Simioni[1], Alice Cani[2], Alberto M. Martelli[3], Giorgio Zauli[1,4], Ayman A.M. Alameen[1], Silvano Capitani[1,5], Luca M. Neri[1]

[1] Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy - [2] Department of Neurosciences, University of Padua, Padua Italy - [3] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy - [4] Institute for Maternal and Child Health, IRCSS "Burlo Garofalo", Trieste, Italy - [5] LTTA Center, University of Ferrara, Ferrara, Italy

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive neoplastic disorder of T lymphocytes characterized by a poor clinical outcome, especially for relapsed patients [1]. The PI3K/Akt/mTOR signaling pathway is crucial for cell growth and survival in many types of solid and blood tumors, including T-ALL, influencing the response to therapeutic treatments [2]. The PI3K/Akt/mTOR network is often hyperactivated in T-ALL and therefore could constitute a target of inhibitory strategies, such as those that use small molecules inhibitors (SMI). The combined administration of multiple drugs is an attractive attempt to overcome drug resistance and to improve clinical outcome [3]. We tested in a panel of T-ALL cell lines three drugs directed against Akt with totally different modes of action: GSK690693, ATP-competitive, MK-2206, allosteric, and Perifosine, alkylphospholipid-Akt inhibitor. We showed that multiple Akt inhibition with this drug combination in T-ALL cell lines was cytotoxic and displayed a synergistic effect which was also related to the timing and the sequence of every drug administration. In fact, our findings showed that 6h of Perifosine pre-treatment followed by the combined administration of MK-2206 and GSK690693 for 30 min was necessary for the complete switch off of the activated protein. This combination caused a potent cell cycle arrest in G0/G1 phase and induced apoptosis and autophagy with more efficacy than single or double drug administration. In conclusion, our data demonstrated that this pharmacological strategy could represent a new promising treatment for patients affected by T-ALL with hyperactivated PI3K/Akt/mTOR signaling pathway.

References

[1] Inaba H., et al. (2013) Acute lymphoblastic leukaemia. Lancet. 2013; 381:1943-1955.
[2] Rodon J., et al. (2013) Development of PI3K inhibitors:lessons learned from early clinical trials. Nature reviews Clin Oncol. 2013; 10:143-153.
[3] Martelli AM., et al. (2014) Targeting signaling pathways in T-cell acute lymphoblastic leukemia initiating cells. Adv Biol Regul. 2014;56:6-21.

Keywords

T-acute lymphoblastic leukemia; Akt; Perifosine; GSK690693; MK-2206.