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Combination of imatinib and clotrimazole enhances cell growth inhibition in T47D breast cancer cells

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Imatinib mesylate (IM), a tyrosine kinase inhibitor, is used as targeted cancer therapy. However, monotargeting by IM does not always achieve full tumor eradication and thus it is recommended to combine IM with other anticancer agents. Clotrimazole (CLT) is an antifungal azole derivative with promising anticancer effects due to inhibiting the activity of glycolytic enzymes. The present study aimed to evaluate the effect of combining CLT with IM on breast cancer cell line in an attempt to establish effective new combination. T47D human breast cancer cell line was treated with different concentrations of IM and/or CLT for 48 h. IM–CLT interaction was determined by isobologram equation and combination index. Cell viability was confirmed by measuring LDH activity. As indicators of glycolysis inhibition, the expression of hexokinase-2 (HK-2) and 6-phosphofructo-1-kinase (PFK-1) plus the activity of intracellular lactate dehydrogenase (LDH) and pyruvate kinase (PK) were determined. In addition, glucose consumption and adenosine triphosphate (ATP) production were measured. Moreover, nitric oxide (NO), vascular endothelial growth factor (VEGF) and hypoxia inducible factor-a (HIF-a) were also determined as they are modulators for glycolysis. This study demonstrated that IM or CLT synergistically inhibited cell growth in T47D as shown by combination and dose reduction indices. The combination of 15 μM IM and 20 μM CLT significantly decreased glucose consumption, activity of both PK and intracellular LDH, while increased leaked LDH, VEGF and NO in the medium compared to each drug alone. Furthermore the combination decreased gene expression of HK-2, PFK-1 and ATP content compared to the control. In conclusion, the synergistic effect of CLT on IM cytotoxicity in T47D cell line maybe mediated through inhibition of glycolysis and increasing both NO and VEGF. Further studies are required to confirm the efficiency and safety of this combination.

Biography

Tarek Mohamed Kamal Motawi, Professor of Biochemistry, Faculty of Pharmacy, Cairo University. Egyptian, date of birth 6/3/1955. Ph.D. in Pharmaceutical Sciences, 1984; M.Sc. in Pharmaceutical Sciences, 1979; B.Sc. in Pharmaceutical Sciences, Faculty of Pharmacy, Cairo University, 1976. Professional experience: Instructor; 1976, Lecturer Assistant; 1980, Lecturer,1984; Assistant Professor,1989; Professor,1994; Head of the Department of Biochemistry, Faculty of Pharmacy, Cairo:- 2008-2014.

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