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L-arginine/5-FU combination treatment discriminates for a good cause: Rescuing the normal cells while killing cancerous ones

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In breast cancer therapy, where reducing the adverse effects of chemotherapy is a determinant factor of success especially during pregnancy, modulatory effect of L-arginine on various cancers is still a controversial issue. Therefore, the present study aims to determine the effect of L-arginine combination with 5-fluorouracil (5-FU) on normal and cancer cells. The primary human umbilical vein endothelial cells (HUVECs) and human breast cancer cell line (BT-20) were treated with L-arginine/5-FU to study their effect on cell survival, NO concentration, and glycolytic activity. Moreover, using molecular docking study, L-arginine effect on glycolysis enzymes activity was evaluated. L-arginine/5-FU effect on angiogenesis was also assessed *in vitro* and *in vivo*. Furthermore, L-arginine effect on 5-FU toxicity was assessed by measuring embryo weight. Real-time PCR and zymography were used to evaluate VEGF and MMP2, 9 expression and enzyme activities, respectively. L-arginine/5-FU combination treatment carried out on the primary human umbilical vein endothelial cells (HUVECs) increased cells survival while induced cell death in BT-20. Nitric oxide (NO) concentration assays in both cell lines was showed to be increased. An inhibitory effect of L-arginine on glycolysis enzyme, human glucokinase (HG) was affirmed through molecular docking study and further supported by glycolysis experiment showing glucose and lactate levels decrease in cancer cells but not in normal cells. Angiogenesis induction in HUVECs was confirmed through VEGF and MMP-2, 9 up-regulated gene expressions and increased MMP-2, 9 activities. However, a down-regulation of the above mentioned genes expression was observed in BT-20 treated with each drug alone and in combination. Furthermore, an *in vivo* increased angiogenesis and decreased embryo toxicity was observed under the treatment with the combination of the drugs. Altogether, findings speculate that L-arginine inhibits cell death induced by 5-FU in normal cells by attenuating the adverse effects of 5-FU, while it doesn't do so in cancer cells (BT-20).

Biography

Kamran Mansouri completed his PhD at Tehran University of Medical Sciences, Iran. He is the Head of Department of Molecular Medicine at Kermanshah University of Medical Sciences, Iran. He has published more than 50 papers in reputed journals.

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