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Modulation of Tamoxifen-Induced Cytotoxicity in Breast Cancer Cell Lines by 3-Bromopyruvate

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Abstract : Background: Tamoxifen (TAM) is the most commonly used hormone therapy for the treatment of early and metastatic breast cancer. Although it significantly decreases the tumor recurrence rate and provides an overall benefit, as much as 20–30% of women still relapse during or after long-term therapy. 3-Bromopyruvate (3-BP) is a promising agent with impressive antitumor effects in several models of animal tumors and cell lines. Aim: This study was designed to investigate the combined effect of (TAM) and (3-BP) in breast cancer cells and to explore their molecular interaction via assessment of apoptotic, angiogenic, and metastatic markers. Methods: In vitro cytotoxicity study was carried out for both compounds to determine the combination regimen producing a synergistic effect and mechanistic pathways were studied using RT-PCR and western techniques. Moreover, the anti-oncolytic and anti-angiogenic potentials were assessed in mice bearing solid Ehrlich carcinoma (SEC). Results: The combined treatment significantly increased the expressions and protein levels of caspase 7, 9, and 3 and decreased of angiogenic markers VEGF, HIF-1α, and HK2 compared to cells treated with either drug individually. However, there were no significant changes in MMP-2 and MMP-9 protein levels. Interestingly, the in vivo results supported the in vitro findings; there was a decrease in the tumor volume and VEFG using immunohistochemistry in the combination-treated groups compared to either TAM or 3-BP treated one. Conclusion: 3-BP synergizes the cytotoxic effect of TAM by increasing apoptosis and decreasing angiogenesis which makes this combination a promising regimen to be applied clinically.

Keywords : tamoxifen, 3-bromopyruvate, breast cancer, cytotoxicity, angiogenesis
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