2-Methoxyestradiol reverses doxorubicin resistance in human breast tumor xenograft

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Abstract

Purpose 2-Methoxyestradiol (2ME), an endogenous estradiol metabolite, was developed as a novel agent based on its antitumor activity and lack of toxicity. This study was designed to investigate the modulatory effect of 2ME on the antitumor effect of doxorubicin (Dox) in resistant breast tumor xenograft. Resistant MCF-7/Dox cells were implanted subcutaneously in nude mice

Methods Treatment with Dox 5 mg/kg, 2ME 30 mg/kg and their combination continued twice a week for 2 weeks.

Results Following 28 days from starting the treatment with Dox alone, the change in tumor volume from first day of treatment was 455.6 ± 16.2%. Combined Dox and 2ME treatment significantly reduced tumor volume to 20.8 ± 43%. Also, combined therapy resulted in enhanced tumor apoptotic and reduced proliferative activities relative to Dox alone. The apoptotic indices were 0.13 ± 0.03 and 0.75 ± 0.06 in Dox alone and Dox + 2ME groups, respectively. For Dox alone group, expression of the proliferative markers PCNA and Ki67 were 0.78 ± 0.06 and 0.63 ± 0.18, respectively. They were significantly reduced to 0.28 ± 0.1 and 0.12 ± 0.1 for their corresponding combined Dox and 2ME group. Interaction analysis clearly indicated that 2ME synergies antitumor, apoptotic and anti-proliferative activity of Dox. Examining body weight, hepatic and cardiac histopathology of the different treatment groups revealed no significant signs of toxicity.

Conclusion These findings suggest that 2ME reverses Dox resistance, with benign side effects profile.

Keywords 2-Methoxyestradiol · Doxorubicin · Drug-resistance

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