2-Methoxyestradiol and multidrug resistance: can 2-methoxyestradiol chemosensitize resistant breast cancer cells?

Samar S. Azab · Salama A. Salama · Ashraf B. Abdel-Naim · Amani E. Khalifa · Ebtelah El-Demerdash · Ayman Al-Hendy

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Abstract 2-Methoxyestradiol (2ME), a natural derivative of estradiol, is currently evaluated in clinical trials for breast cancer. The current study aims to evaluate the modulatory effects of 2ME on regulation of multidrug resistance (MDR) in doxorubicin (Dox) resistant breast cancer cells (MCF-7/Dox) and its underlying mechanisms. The chemosensitizing effect of 2ME on Dox cytotoxicity is tested by MTT assay. RT² Profiler PCR Array was used to identify differentially expressed genes in Dox and/or 2ME treatment groups, based on significance of results 4 genes were selected: MDR1, Bcl2, P53 and Cyclin D1. The expression of these genes was confirmed using western blotting. Lastly, functions of these genes were examined by studying p-glycoprotein (p-gp) function, caspase 3 activity and flowcytometric cell cycle assays respectively. 2ME significantly increased sensitivity of the resistant MCF-7/Dox cells to the cytotoxic effect of Dox by 2.9-folds. The array and western blotting showed that Bcl2 and Cyclin D1 expression were down regulated; P53 expression was not affected while MDR1 was over expressed by combination of 2ME with Dox. 2ME increased p-gp function by 24 ± 7.05%, compared to control. Addition of 2ME to Dox increased caspase activity by 27-folds. Combination of 2ME to Dox arrested the cell cycle in G1 and S phases, compared to Dox. In conclusion, 2ME chemosensitizes resistant breast cancer cells to Dox cytotoxicity by down regulating expression of Bcl2 and Cyclin D1, augmenting caspase 3 activity as well as inducing cell cycle block in G1 and S phases.

Keywords Doxorubicin · 2-Methoxyestradiol · Multi-drug resistance