Oncofertility: Effect of chemotherapeutics and gamma tocopherol (gT) on breast cancer and primary-derived ovarian cells

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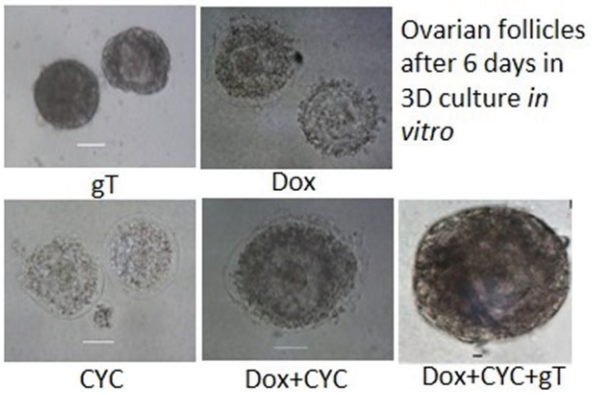
Statement of the Problem: Premenopausal breast-cancer patients are treated with a combination of chemotherapeutics, commonly doxorubicin (adriamycin) and cyclophosphamide ('AC'), but the combined toxicity of 'AC' *in vitro* has not been reported. Additionally, 'AC'-treated breast cancer survivors suffer premature ovarian failure and adverse effects caused by estrogen (E2) depletion. Each chemotherapeutic generates reactive oxygen species (ROS). Gamma- tocopherol (gT), a constituent of antioxidant Vitamin E, has anticancer activity. The aims were to examine the hypotheses that exposing a human breast cancer cell-line (MCF7) to AC+gT would reduce ROS, but gT would maintain anti-cancer activity. Secondly, that AC+gT would be less cytotoxic to primary-derived ovarian cells than 'AC'.



Methodology & Findings: MCF7 cells were exposed to doxorubicin (Dox), 4-hydroxyperoxy-cyclophosphamide (CYC), Dox+CYC, gT, and Dox+CYC+gT *in vitro*. Doxorubicin, and gT, but not CYC, caused dose- dependent cytotoxicity. Dox+CYC caused significant cytotoxicity similar to doxorubicin alone. Dox+CYC+gT caused significantly more MCF7-cell death than Dox+CYC.

Follicles (an egg surrounded by proliferating cells) from mouse ovaries were cultured in Matrigel. Follicle diameters and E2 synthesis increased under control conditions. The percentages of viable cells per follicle after 6d in 0.3% DMSO solvent control (for gT) were 60±9%, and 57±14% after exposure to the MCF7-derived EC25 value for gT. Exposure to the MCF7-derived EC25 values for Dox+CYC resulted in 16±5% ($p<0.05$, 37% of control), whereas Dox+CYC+gT (MCF7:EC25+EC25+EC25) resulted in 44±7% viable cells per follicle (74% of control).

Conclusion & Significance: Hypotheses were supported: gT increased Dox+CYC cytotoxicity against MCF7 cancer cells but decreased Dox+CYC cytotoxicity towards primary-derived proliferating ovarian cells. gT anti-cancer mechanism of action requires elucidation, but antioxidant activity may protect follicles against chemotherapeutic cytotoxicity.

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