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# Combined Treatment of Estrogen-Receptor Positive Breast Microtumors with 4-Hydroxytamoxifen and Novel Non-Steroidal Diethyl Stilbestrol-Like Analog Produces Enhanced Preclinical Treatment Response and Decreased Drug Resistance

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**Abstract :** This research is a pre-clinical assessment of anti-cancer effects of novel non-steroidal diethyl stilbestrol-like estrogen analogs in estrogen-receptor positive/ progesterone-receptor positive human breast cancer microtumors of MCF 7 cell line. Tamoxifen analog formulation (Tam A1) was used as a single agent or in combination with therapeutic concentrations of 4-hydroxytamoxifen, currently used as a long-term treatment for the prevention of breast cancer recurrence in women with estrogen receptor positive/ progesterone receptor positive malignancies. At concentrations ranging from 30-50 microM, Tam A1 induced microtumor disaggregation and cell death. Incremental cytotoxic effects correlated with increasing concentrations of Tam A1. Live tumor microscopy showed that microtumos displayed diffuse borders and substrate-attached cells were rounded-up and poorly adherent. A complete cytotoxic effect was observed using 40-50 microM Tam A1 with time course kinetics similar to 4-hydroxytamoxifen. Combined treatment with TamA1 (30-50 microM) and 4-hydroxytamoxifen (10-15 microM) induced a highly cytotoxic, synergistic combined treatment response that was more rapid and complete than using 4-hydroxytamoxifen as a single agent therapeutic. Microtumors completely dispersed or formed necrotic foci indicating a highly cytotoxic combined treatment response. Moreover, breast cancer microtumors treated with both 4-hydroxytamoxifen and Tam A1 displayed lower levels of long-term post-treatment regrowth, a critical parameter of primary drug resistance, than observed for 4-hydroxytamoxifen when used as a single agent therapeutic. Tumor regrowth at 6 weeks post-treatment with either single agent 4-hydroxy tamoxifen, Tam A1 or a combined treatment was assessed for the development of drug resistance. Breast cancer cells treated with both 4-hydroxytamoxifen and Tam A1 displayed significantly lower levels of post-treatment regrowth, indicative of decreased drug resistance, than observed for either single treatment modality. The preclinical data suggest that combined treatment involving the use of tamoxifen analogs may be a novel clinical approach for long-term maintenance therapy in patients with estrogen-receptor positive/progesterone-receptor positive breast cancer receiving hormonal therapy to prevent disease recurrence. Detailed data on time-course, IC50 and tumor regrowth assays post- treatment as well as a proposed mechanism of action to account for observed synergistic drug effects will be presented.

**Keywords :** 4-hydroxytamoxifen, tamoxifen analog, drug-resistance, microtumors
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