Preclinical breast cancer biology

97P AT-101 (-/- GOSSYPOL) IN COMBINATION WITH TRASTUZUMAB TRIGGERS APOPTOSIS THROUGH INHIBITING BCL-2, BCL-XL AND MCL-1 PROTEIN LEVELS IN HUMAN HER2-POSITIVE BREAST CANCER CELLS

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Introduction: AT-101, the (-/-) enantiomer of gossypol, inhibits the Bcl-2 family proteins which contain BH3 domain. Trastuzumab is a monoclonal antibody that interferes with the HER2 receptor, is widely used in HER2-overexpressing breast cancer. In the present study, we have investigated the possible synergistic cytotoxic and apoptotic effects of AT-101 in combination with Trastuzumab in HER2-positive human breast cancer cell line, MDA-MB-453. Moreover, expression levels of Bcl-2, Bcl-XL and Mcl-1 proteins, which are the main players of the intrinsic apoptosis pathway, were investigated during the exposure of this combination treatment.

Methods: Cytotoxicity was assessed by XTT cell viability assay. Apoptosis was shown by measuring DNA fragmentation and caspase 3/7 enzyme activity. Mitochondrial membrane potential was demonstrated by TMRE staining. Expression levels of Bcl-2, Bcl-XL and Mcl-1 proteins were investigated by western blot analysis.

Results: AT-101/Trastuzumab combination (80 µg/mL TB + 2.5 µM AT-101, 72h) was shown to have strong synergistic cytotoxic effects at clinically achievable doses. Combined treatment also induced DNA fragmentation, caspase 3/7 activation and mitochondrial membrane potential dissipation. Moreover, Bcl-2, Bcl-XL and Mcl-1 protein levels were reduced after combination treatment exposure, showing an intrinsic induction of apoptosis by this novel drug combination.

Conclusions: Synergistic combination of AT-101 and Trastuzumab might be a novel candidate for the treatment of HER2-overexpressing breast cancer and preliminary results of our study provide an important mechanistic rationale.

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