A DIVERSE INDUCTION OF APOPTOSIS BY TRABECTEDIN IN MCF-7 (HER2-/ER+) AND MDA-MB-453 (HER2+/ER-) BREAST CANCER CELLS

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Introduction: Trabectedin (Yondelis; ET-743), a semi synthetic tetrahydroisoquinoline alkaloid that was originally derived from the marine tunicate Ecteinascidia turbinata, binds to the minor groove of DNA. It is a strong apoptotic agent; however its apoptotic mechanisms are not well defined in cancer cells. Breast cancer, is a heterogenic disease in cellular and molecular levels. The objective of this study is to investigate whether trabectedin mediated apoptosis shows any diversity in human breast cancer cell lines with different genotypes.

Materials and Methods: MCF-7 (HER2-/ER+) and MDA-MB-453 (HER2+/ER-), representatives of different molecular subtypes in breast cancer, were used. Cytotoxicity was assessed by XTT cell viability assay. Apoptosis was shown by measuring both DNA fragmentation and mitochondrial membrane potential. Changes in apoptosis-related protein expressions were investigated by apoptosis antibody array.

Results: Trabectedin induced cytotoxicity and apoptosis in breast cancer cells in a time and dose dependent manner. The expression levels of the death receptor pathway molecules, such as TRAIL R1/DR4, TRAIL R1/DR5, TNF R1/TNFRSF1A, FADD and phospho-p53 were significantly increased in MCF-7 cells, whereas, the mitochondrial pathway related proteins Bax, Bad, Cytochrome-c, Smac/diablo, Htra2/Omi, and Cleaved caspase-3 were increased in MDA-MB-453 cells by trabectedin exposure.

Conclusion: We have shown that trabectedin mediated apoptosis causes selective activation of extrinsic and intrinsic pathways in two genotypically different breast cancer cells. This preliminary data might guide clinicians to choose appropriate combination agents with trabectedin based on different molecular subtypes of breast cancer. The intimate investigation of anticancer agents by molecular research will let more tailored treatment in near future.