THE SYNERGISTIC EFFECT OF TYROSINE KINASE INHIBITORS AND DOXORUBICIN IN TRIPLE-NEGATIVE BREAST CANCER

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Triple-negative breast cancer (TNBC) lacks chemotherapeutic targets, which makes it difficult to find alternative treatments. One of the drugs used in TNBC therapy is doxorubicin (DOX) also tyrosine kinase inhibitors (TKIs) are promising agents. Even though these compounds exhibit anti-cancer efficacy, drug resistance might develop due to efflux pump, cellular microenvironment and other mechanisms [1]. Synergistic effect of compounds acting by different pathways is one of the approaches to overcome drug resistance [2]. Therefore in this study we selected five most active sunitinib derivatives EMAC4001, 4006, 4007, 4008, 4017 synthesized at Cagliari University, Italy [3]. The aim of this study was to determine sunitinib and its analogues activity in combination with DOX on TNBC cells.

As a model cell lines for our research, human TNBC cell line MDA-MB-231 (WT) and DOX-resistant (DR) MDA-MB-231 were used. Compound effect on cell viability was measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay after 72 h of incubation. The half-maximal effective concentrations (EC50) were calculated using Hill equation. The activity of selected sunitinib and its derivatives in combination with DOX (1:1) was determined by calculating fraction affected (fa) versus combination index (CI) plots based on Chou-Talalay methodology [2]. MDA-MB-231 DR cell line was more resistant to all tested drugs than MDA-MB-231 WT. Sunitinib analogue EMAC4001 reduced cell viability the most among tested TKIs (EC50 105.7 ± 18.5 nM in MDA-MB-231 WT and 690.3 ± 158.9 nM in MDA-MB-231 DR). CI index showed that all combinations, except sunitinib and EMAC4007, had synergistic effect on MDA-MB-231 DR cells at fa = 0.5 (CI < 1).

Based on results, TKI and DOX combinations may be considered a promising chemotherapeutic agent against drug resistant TNBC.

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