CARDIO-ONCOLOGIA E CARDIO-TOSSICITÀ ***52***
CARDIOTOSSICITA' DA FARMACI ***(CARDIO-ONCOLOGIA E CARDIO-TOSSICITA')***
DIAGNOSI, PREVENZIONE E TRATTAMENTO DELLA CARDIOTOSSICITA' ***(CARDIO-ONCOLOGIA E CARDIO-TOSSICITA')***
FARMACI ANTI-DIABETICI ***(DIABETE E MALATTIE DEL METABOLISMO)***

LOW DOSES OF DAPAGLIFLOZIN REDUCES ANTHRACYCLINE AND TRASTUZUMAB-INDUCED CARDIOTOXICITY THROUGH MYD88, NLRP3 AND MTORC-1 MEDIATED PATHWAYS.

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Introduction: The clinical trial "DECLARE-TIMI 58" (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), demonstrated that dapagliflozin, a Sodium glucose cotransporter 2 inhibitor, reduces the composite end point of cardiovascular death/hospitalization for heart failure in a broad population of patients with type 2 diabetes mellitus.
Purpose: We aimed to study if dapagliflozin could exerts cardioprotective effects in doxorubicin and trastuzumab-induced cardiotoxicity through the analysis of multiple biochemical mechanisms.
Methods: HL-1 adult cardiomyocytes were exposed to subclinical concentration of doxorubicin and trastuzumab (100 nM) alone or in combination with dapagliflozin at 50 nM. Determination of cell viability was performed through analysis of mitochondrial dehydrogenase activity and the study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxynonenal), and of intracellular Ca2+ homeostasis by spectrophotometric methods . Moreover, anti-inflammatory studies were also performed (activation of NLRP3 inflammasome; expression of TLR4/MyD88; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins 1β, 8 and 6). Moreover, mTORC1 /Fox01/3a expression studies were performed through western blot and confocal laser microscope methods.
Results: Dapagliflozin increases significantly the cardiomyocytes viability during exposure to doxorubicin and trastuzumab. Its cardioprotective properties are explainable by the reduction of intracellular Ca2+ overload (-47,6% vs cells treated only to anticancer drugs; $p<0,001$), of the lipid peroxidation phenomena (mean reduction of 35-43 % compared to cells exposed only to anticancer drugs; $p<0,001$). Moreover, cardiomyocytes exposed to dapagliflozin during anticancer drugs have a reduced expression of pro-inflammatory cytokines involved in cardiotoxicity (- 37,3 % for Interleukin-1β; -39,5 for Interleukin 8 ; -41,3 % for Interleukin 6 ; $p<0,001$ for all). Notably, dapagliflozin reduces p65-NF-κB activation (- 36,5% vs cells treated only to anticancer drugs) and inhibits of 27,8 % the expression of NLRP3 inflammasome. mTORC1 /Fox01/3a expression were also reduced after treatment with dapagliflozin, an aspect directly involved in the reduction of cardiomyocyte apoptosis
Conclusion: Dapagliflozin demonstrated for the first time cardioprotective properties during doxorubicin and trastuzumab exposure. The main biochemical effects of dapagliflozin are related to MYD88, NLRP3 complex, Leukotrienes/Interleukin 6 axis and mTORC1 mediated apoptosis. This study provides the proof of concept for translational studies designed to investigate the cardioprotective use of dapagliflozin in preclinical models of cardio-oncology.