conferenceseries.com

World Congress on CARDIOLOGY & HEART CONGRESS AND SURGERY

May 28, 2021 | Webinar

The effect of losartan, mirabegron and their combination on the development of doxorubicin-induced chronic cardiotoxicity

Marah Freiwan

Interdisciplinary Center of Excellence, University of Szeged, Hungary

Statement of the problem: Doxorubicin (DOXO) causes dose□dependent cardiotoxicity years to decades after breast cancer or lymphoma treatment. Losartan is an angiotensin-II receptor blocker commonly used to prevent cardiac remodeling in various co-morbidities. The beta-3 adrenergic receptor agonist mirabegron attenuates hypertension-induced cardiac remodeling. Therefore, here we investigated the effects of losartan, mirabegron, and their combination on the development of DOXO-induced cardiotoxicity.

Methods: Male Wistar rats (350-400g) were divided into 5 experimental groups and followed-up for 11 weeks: 1) control group treated with saline (ip. 6x1 mL//kg) and tap water (from the 5th week), 2) DOXO group (ip. 6x1.5 mg/kg DOXO) treated by tap water (per os 2 mL/kg) from week 5, 3) DOXO group treated by losartan (per os 20 mg/kg/day from week 5), 4) DOXO group treated by mirabegron (per as 30 mg/kg/day from week 5), and 5) DOXO group treated by the combination of losartan and mirabegron from week 5. At week 11, transthoracic echocardiography was performed to monitor cardiac morphology and function. Then left ventricles were prepared for histological and qRT-PCR measurements.

Findings: In the DOXO group, chronic cardiotoxicity developed, which is characterized by reduced systolic LV wall thicknesses, ejection fraction, diastolic dysfunction, and LV fibrosis. Losartan failed to improve these parameters significantly; however, mirabegron and the combined treatment markedly improved them. The LV overexpression of Smad3 was significantly reduced by mirabegron and the combination treatment. Interestingly, the LV overexpression of IL-1b and IL-6 was significantly decreased by losartan and mirabegron, but not the combination treatment.

Conclusion & Significance: Losartan failed to ameliorate the cardiac remodeling in the DOXO group; however, it showed anti- inflammatory properties. Mirabegron is a promising agent in the treatment of DOXO- induced cardiotoxicity via its anti-fibrotic and anti-inflammatory effects. The combination treatment seems to be effective against DOXO-induced cardiac fibrosis and remodeling.

Funding: The work was supported by the projects GINOP-2.3.2-15-2016-00040, NKFIH FK129094, EFOP-3.6.2-16-2017-00006 (LIVE LONGER), and by the Ministry of Human Capacities (20391-3/2018/FEKUSTRAT). MS by the New National Excellence Program of the Ministry of Human Capacities (ÚNKP-20-5-SZTE-166), the János Bolyai Research Fellowship of the Hungarian Academy of Sciences.

Marah.mf.94@gmail.com