400P LCZ 696, administered during doxorubicin, trastuzumab or pertuzumab treatment, prevents cardiotoxicity in our in vitro model

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Background: Doxorubicin (DX), Trastuzumab (T) and Pertuzumab (P) are antineoplastic drugs used in the treatment of breast cancer. Adverse cardiovascular events related to anticancer drugs are among the leading causes of morbidity and mortality in cancer patients. Sacubitril-valsartan (LCZ 696) is a combination drug, made up of neprilysin inhibitor sacubitril and angiotensin II receptor blocker valsartan, used for the treatment of heart failure in patients with a reduced ejection fraction. Here, we aim to assess whether LCZ 696, administered during DX, T or P treatment, reduces *in vitro* anticancer drugs-related cardiotoxicity compared to Valsartan (V), used as a control drug.

Methods: The H9C2 rat cardiomyoblasts were seeded in 96-well plates at a density of 1 x 10^4 cells/well and incubated at 37 °C with 5% CO2 for 16 hours. After the addition of 200 nM of T, P or DX in the culture medium, cells were incubated for 72 hours. The cells were further treated in the absence or presence of 10 μM of LCZ 696 or V for additional 3 days. Viable cells were counted by trypan blue exclusion test and cell survival was expressed as percentage of viable cells compared to control untreated cells.

Results: LCZ 696 reduced significantly T, P and DX related toxicity in H9C2 cardiomyoblasts as evidenced by the higher percentage of viable cells treated with combinations of T, P or DX with LCZ 696 with respect to cells treated with T, P or DX alone ($p < 0.001$). V reduced significantly T and DX related toxicity in H9C2 cardiomyoblasts treated with combinations of T or DX and V with respect to the cells treated with T or DX, used as single agents ($p < 0.001$). However there was no significant reduction of toxicity when H9C2 cells were treated with P + V. Thus, both LCZ 696 and V reduced significantly DX and T related toxicity when administered to H9C2 cardiomyoblasts after the antineoplastic treatment (no significant difference between LCZ 696 and V treatment, $p = 0.6$). Moreover, LCZ 696 was significantly more effective than V ($p < 0.001$) in reducing both T and P related toxicity when administered to cultures of H9C2 cardiomyoblasts after antineoplastic treatments.

Conclusions: LCZ 696, administered during DX, T or P treatment, significantly increases the viability of treated cells, thus reducing cardiotoxic effects of these drugs, as demonstrated by our *in vitro* experiments. The future perspective aims to test LCZ 696 in *in vivo* models to assess its capability to blunt left ventricular dysfunction after antineoplastic treatments.

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