Trastuzumab cardiomyopathy is prevented by the administration of Ranolazine at the end of antineoplastic treatment: in vitro and in vivo study

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Background: The anti-cancer anti-ErbB2 Trastuzumab (T) is used to treat HER2 positive breast cancer, but can produce cardiac dysfunction. The late INa inhibitor Ranolazine (R) protects from doxorubicin-induced oxidative stress and cardiac dysfunction. We aim at assessing whether R, administered after T treatment, reduces T cardiotoxicity in vivo and in vitro.

Methods: In vitro, rat H9C2 cardiomyoblasts and human fetal cardiomyocytes were treated with T for 3 days and then treated in the absence or presence of R for 3 days. Cell viability was determined by cell counts and MTT assays. In vivo, fractional shortening (FS) and ejection fraction (EF) were measured by M mode echocardiography and radial and longitudinal strain (RS and LS) were measured using 2D-Speckle Tracking, in C57/BL6 mice, at 0, 2 and after 7 days of daily administration of T. These measurements were repeated after 5 days of R treatment initiated at the end of T treatment. We have divided mice in 4 groups. The first group (G1) was treated with T for 7
days. The second group (G2) was treated with T for 7 days and then treated with R for 5 days. The other 2 were control groups: CG1 (sham) and CG2 (no R).

Results: R reduced T toxicity in H9C2 cardiomyoblasts and human fetal cardiomyocytes as evidenced by higher percentage of viable cells treated with T+ R with respect to cells treated with T alone (p<0.01). In vivo, after 7 days with T, FS decreased to 48.7±4.1%, p<0.01 vs 62.3±0.8% (sham), EF to 81.8±3.5%, p<0.01 vs 91.7±0.5% (sham), RS to 21±8.1%, p<0.01 vs 43.2±4% (sham), and LS to -11±3.7%, p<0.01 vs -38.8±6% (sham). In mice treated with R for 5 days after T treatment, the indices of cardiac function recovered: FS was 61±1.2%, EF was 91±0.7%, p<0.01; RS was 35±1.8%, p<0.05 vs T. However the alteration of LS persisted after treatment with R (-15.4±5.1%, p=0.3 vs T). R prevents the increased expression of BNP (p<0.05) on heart tissue. In lysates from murine hearts, R reduced apoptosis as evidenced by decreased levels of cleaved caspase 3.

Conclusions: R post-treatment reduces cardiotoxic effects due to T as demonstrated in vitro by higher percentage of viable cells and in vivo by the normalization of the values of FS, EF and RS and by the reduction of apoptosis on heart tissue.