basic science

RANOLAZINE BEFORE AND DURING TRASTUZUMAB TREATMENT, PREVENTS CARDIOTOXICITY IN MICE

N. Maurea1, C. Coppola2, G. Piscopo2, D. Rea2, F. Galletta2, C. Maurea2, I. Capasso4, C. Arra3, R.V. Iaffaioli5

1Cardiology, INT Pascale Naples, Naples, ITALY
2Cardiology, National Cancer Institute, Pascale Foundation, Naples, ITALY
3Animal Experimental Research, National Cancer Institute, Pascale Foundation, Naples, ITALY
4Breast Oncology Division, National Cancer Institute, Pascale Foundation, Naples, ITALY
5Colorectal Oncology, National Cancer Institute, Pascale Foundation, Naples, ITALY

Aim: ErbB2 is overexpressed in about 25% of breast cancers. It modulates myocardial development and function in the heart. Trastuzumab (T), an anti-ErbB2 inhibitor, has improved the prognosis of patients with breast cancer, but is related to an increased risk of asymptomatic left ventricular (LV) dysfunction (3–34%) and heart failure (2–4%). The mechanisms of T cardiotoxicity are not entirely known and can include changes in Ca2+ regulation related to blockade of ErbB2. Here, we aim at assessing whether ranolazine (RAN), diminishing intracellular Ca2+ through its inhibition of late Ina, blunts T cardiotoxicity in vivo.

Methods: To evaluate cardiac function in vivo, fractional shortening (FS) and ejection fraction (EF) were measured by echocardiography M-Mode in C57BL6 mice, 2-4 mo old, pretreated with RAN (750mg/kg/day, a dose comparable to the one used in humans) per os for 3 days. RAN was then administered for additional 7 days, alone and together with T (2.25 mg/kg/day ip), according to our well established protocol.

Results: In our in vivo studies, after 7 days with T, FS decreased to 49 ± 1.5%, p < 0.01 vs 60 ± 0.5% (sham), and EF to 81 + 2%, p < 0.01 vs 91 ± 1% (sham). RAN alone did not change FS (59 ± 2%) nor EF 89 ± 1%. Interestingly, in mice treated with RAN and T, RAN prevents the reduction of EF and FS vs T alone (FS was 58 ± 1%, EF was 90 ± 1%, p = 0.01 and p < 0.01 respectively).

Conclusions: In our mouse model, T produces LV dysfunction and RAN blunts T cardiotoxic effects. We plan to test RAN as a cardioprotective agent with other target-therapy drugs in our experimental models and to define the mechanisms of cardioprotection.

Disclosure: All authors have declared no conflicts of interest.