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Cardiotoxic effects, or lack thereof, of anti-ErbB2 immunoagents.

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Background: Herceptin (H), an anti-ErbB2 humanized antibody prescribed for treatment of ErbB2-positive breast cancer, has proved to be an essential tool in immunotherapy. However, large-scale clinical studies with H have shown that it engenders cardiomyopathy, particularly in patients treated either concurrently or previously with anthracyclines. Two novel human antitumor immunoconjugates were engineered in our laboratory by fusion of a human anti-ErbB2 scFv, Erbicin, with either a human RNase or the Fc region of a human IgG1, and thus called Erb-hRNase and Erb-hcAb (human anti-ErbB2-compact antibody), respectively. Both immunoagents are selectively cytotoxic for ErbB2-positive cancer cells in vitro and vivo. The Erbicin-derived immunoagents (EDIA) target on breast cancer cells an ErbB2 epitope different from that of H. We report that EDIA did not show in vitro cardiotoxic effects on rat and human cardiomyocytes, whereas H was strongly toxic.

Methods: Methods for measuring cardiac function

in M-mode with shortening fraction (FA) and in B-mode with ejection fraction are not very sensitive in detecting early myocardial damage. In this study we evaluated myocardial strain by speckle tracking technique (ST) by Color Doppler echocardiography (Visual sonic Vevo 2100) to identify early left ventricular dysfunction in mice treated with EDIA, doxorubicin (D), H, their associations and in a sham group. We measured ST and FA by assessing M-mode short axis projection in C57BL/6 mice at time 0, 2 and 6 days of daily administration.

Results: EDIA did not impair cardiac function in vivo in a mouse model whereas H significantly reduced radial strain at 3 days of treatment and fractional shortening (% FS) at 6 days of treatment compared to the sham group in a fashion similar to D. Similarly, cardiac fibrosis, an index of collagen accumulation following cardiac muscle deterioration, was significantly attenuated in mice treated with either Erb-hcAb or Erb-hRNase as compared to those treated with H or D.

Conclusions: These results suggest that the Erb-hcAb and the immuno RNase are immunoagents which can fulfil the therapeutic need of patients ineligible to H treatment due to cardiac dysfunction