Randomized trial of lisinopril or carvedilol for the prevention of cardiotoxicity in patients with early stage HER2-positive breast cancer receiving trastuzumab

P.N. Münster1, J. Krischer2, R. Tamura2, L. Bello-Maticaria2, A. Fink2, W. McCaskill-Stevens2, M. Guglin2

1Medicine, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 2Health Informatics Institute, University of South Florida, Tampa, FL, USA.

Background: Trastuzumab is an integral part of therapy for patients with HER2-positive breast cancer. Yet, cardiac side effects, particularly in patients who receive anthracyclines require frequent monitoring and result in dose interruptions and discontinuation of trastuzumab. Prophylactic use of angiotensin converting enzyme inhibitors or beta blockers may prevent cardiotoxicity associated with chemotherapy and trastuzumab.

Methods: In a large prospective double-blind, placebo-controlled trial, the rates of pre-specified cardiotoxicity and trastuzumab interruptions were evaluated in patients with early stage HER2 positive breast cancer treated with one year of trastuzumab. Patients were randomized to simultaneously receive either the ACE inhibitor, lisinopril, or beta-blocker, carvedilol, or placebo and were stratified by anthracycline use.

Results: The study included 468 eligible patients (median age: 51, BMI 27 kg/m², baseline systolic BP: 126 mmHg and LVEF: 63 ± 6.29%) from 127 community-based practices. Both interventions reduced trastuzumab interruptions (p = 0.01). For patients receiving an anthracycline, cardiac event rates were higher in the placebo group (47%), compared to lisinopril (37%), and carvedilol (31%). Interruptions of trastuzumab were required in 23% patients on lisinopril and 20% on carvedilol compared to 40% on placebo (p = 0.007). Changes in LVEF from baseline (least square means, SE) were significantly reduced with both carvedilol (-4.5 (0.8), p = 0.008, and lisinopril (-4.0 (0.8), p = 0.002) than placebo, (-7.7 (0.8). Cardiotoxicity-free survival was longer on both carvedilol (hazard ratio 0.49, 95% confidence intervals 0.27, 0.89, p = 0.009) or lisinopril (HR 0.53, CI 0.30, 0.94, p = 0.015). Cardiac events for patients treated with non-anthracycline containing regimens were similar for all groups with no difference in number of trastuzumab interruptions.

Conclusions: Both lisinopril and carvedilol prevented cardiotoxicity in patients with HER2-positive breast cancer treated with trastuzumab and anthracyclines. The use of lisinopril or carvedilol should be considered to offset cardiac events and to minimize interruptions of trastuzumab.

Clinical trial identification: NCT01009918.

Legal entity responsible for the study: National Cancer Institute, Community Oncology and Prevention Trials Research Group, Rockville, MD.

Funding: National Cancer Institute, Community Oncology and Prevention Trials Research Group, Rockville, MD.

Disclosure: All authors have declared no conflicts of interest.