Cardioprotective effect of Trimetazidine in patients with early breast cancer receiving anthracycline-based chemotherapy

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Funding Acknowledgement: Type of funding source: None

Background: Anthracyclines, alone or in combination with other drugs, are among the most effective chemotherapeutic agents to treat breast cancer both in the adjuvant and neoadjuvant settings. Unfortunately, anthracycline-associated dose-dependent cardiotoxicity is a limiting factor in clinical use. Extensive efforts have been devoted to identifying strategies to prevent anthracycline-induced cardiotoxicity. However, most cardioprotective agents have shown little efficacy in clinical trials. We hypothesized that myocardial damage by anthracyclines could be rationally prevented by using trimetazidine (TMZ), previously reported to interfere with anthracycline- and trastuzumab-induced cardiotoxicity. Therefore, we planned a randomized, controlled, open trial to determine whether TMZ may prevent the development of left ventricular (LV) dysfunction in patients receiving standard treatment for breast cancer.

Methods: The trial included 73 patients (41.2±8.1 years) undergoing surgery for breast cancer, who were scheduled for adjuvant epirubicin-containing chemotherapy and, if indicated, trastuzumab. Patients were randomly allocated in a 1:1 ratio to receive TMZ or baseline therapy only (control group). The main study endpoint was a reduction in the deterioration of left ventricular ejection fraction (LVEF), as evaluated by serial echocardiography performed at randomization and then every 3 months after the start of chemotherapy and for 1 year after its completion. Secondary outcome measures included echocardiographic indices of LV diastolic dysfunction, structural myocardial alterations, as assessed by speckle tracking echocardiography, and changes in cardiac biomarkers (troponin and brain natriuretic peptide).

Results: We found no significant differences between the two groups regarding baseline clinical and echocardiographic parameters. The two groups reached a similar cumulative dose of doxorubicin. No patient died during the study and no patients withdrew from chemotherapy. Three months after the start of chemotherapy, nonsignificant changes were observed in LVEF, shortening fraction, and LV diameters. No significant changes in cardiac biomarkers were observed in either group. Tissue Doppler imaging detected a significant decrease in myocardial velocities (P=0.001) in the control group, indicating LV diastolic dysfunction. In the same group, speckle tracking imaging revealed a statistically significant alteration in ventricular deformation (P=0.01), which means a decrease in LV systolic function. In the TMZ group, no significant alterations in LV diastolic function were observed.

Conclusions: Tissue Doppler imaging and speckle tracking imaging are more sensitive than conventional echocardiograms in the early diagnosis of cardiac dysfunction and TMZ seems to have an important role in the prevention of cardiotoxicity.