Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Primary Results of a Randomized, 2 x 2 Factorial, Placebo-Controlled, Double-Blind Clinical Trial


Introduction:
Contemporary adjuvant therapy regimens for early breast cancer are associated with improved survival but at the cost of increased risk of cardiac dysfunction that may progress to clinical heart failure. Preventive neurohormonal blockade may alleviate the decline in cardiac function, but results from randomized, placebo-controlled, double-blind trials are missing.

Hypothesis:
We tested the hypothesis that cardiotoxicity in patients receiving adjuvant treatment containing anthracyclines with or without trastuzumab and radiation for early breast cancer can be prevented by the concomitant use of the beta-blocker metoprolol and/or angiotensin receptor blocker candesartan.

Methods:
PRADA (NCT01434134) is a 2x2 factorial, randomized, placebo-controlled, double-blind clinical trial evaluating the cardioprotective effect of metoprolol succinate and/or candesartan cilexetil vs. placebo administered in parallel with adjuvant anti-cancer therapy. The target dose was 100 mg daily for metoprolol and 32 mg daily for candesartan. Between September 2011 and September 2014 126 women (mean age 50.7 years) with early breast cancer and no serious concomitant illness were validly randomized at a single center. The duration of adjuvant therapy ranged from 10 to 61 weeks. The primary endpoint was change in left ventricular ejection fraction (LVEF) as determined by cardiac magnetic resonance imaging (MRI) from baseline to the completion of adjuvant therapy.

Results:
There was no evidence of an interaction between assignment to candesartan and to metoprolol. In the intention-to-treat analysis, the overall decline in LVEF was 2.6 percentage points (95% confidence interval 1.5 - 3.8) in the placebo group and 0.8 (-0.4 - 1.9) in the candesartan group (p=0.026 for between-group-difference). In the per-protocol analysis the decline was 2.6 (1.4-3.8) percentage points in the placebo group and 0.6 (-0.6-1.8) in the candesartan group (p=0.021 for between-group-difference). No effect of metoprolol on the change in LVEF was observed.

Conclusions:
Concomitant treatment with candesartan, but not metoprolol provides protection against decline in LVEF in women treated for early breast cancer with adjuvant anti-cancer treatment.

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