European Heart Journal Supplements (2023) **25** (Supplement B), B25–B27
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad062

Cardiac toxicity of chemotherapy for breast cancer: do angiotensin-converting enzyme inhibitors and beta blockers protect?

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KEYWORDS
Cardiotoxicity;
Cardiovascular risk;
Prevention

Cardiotoxicity is a relatively frequent and potentially serious side effect of anticancer treatments, particularly anthracyclines and trastuzumab, widely used in the treatment of breast cancer. The increase in cancer survivors has generated a growing interest in the prevention of cardiotoxicity. Although early studies suggested an overall benefit on cardiac function with the use of ACE inhibitors (ACEIs) and beta blockers (BBs), more recent randomized trials have demonstrated little or no effect of pharmacological interventions. Even the various meta-analyses conducted in this area have provided weak results in favour of cardioprotective therapies for which the benefit would not always justify the risk of developing side effects. Given the incompleteness of the evidence, there is no clear consensus on which patients should initiate cardioprotective therapy. As recommended in the new guidelines of the European Society of Cardiology, risk stratification before treatment is crucial to identify high-risk patients who would benefit most from the use of cardioprotective therapy. Randomized trials are currently underway to evaluate other therapeutic strategies such as sacubitril/valsartan, and the possibility of using gliflozins in the future cannot be excluded. However, rigorous control and treatment of risk factors remain the primary focus in the management of these patients.

Introduction

Approximately 4 million women in the United States currently have breast cancer.[1] Advances in anticancer therapies have led to a growing increase in long-term survival and therefore to greater attention to the potential early and late side effects that can reduce the life expectancy of survivors. Cardiovascular disease (CVD) is considered one of the most frequent and potentially serious side effects associated with cancer therapy, which is why there has been a growing interest in cardioprotection strategies and treatment of cardiotoxicity. Overall, all-cause mortality increased 3.8-fold in cancer survivors who develop CVD compared with those who do not.[2] One of the mainstay treatments of breast cancer is anthracycline (AC) and trastuzumab therapy which are known to be associated with a reduction in left ventricular ejection fraction (LVEF). The term cardiotoxicity has been commonly used to refer to decreased left ventricular (LV) systolic function and/or the development of clinical heart failure and is often used interchangeably with the term cancer therapy-related cardiac dysfunction (CTRCD). The recently published ESC guidelines have classified cardiotoxicity into symptomatic and asymptomatic and have emphasized the role of global longitudinal strain (GLS) and biomarker dosage in addition to the sole measurement of LVEF for the definition and characterization of risk classes and different forms of cardiotoxicity.[3]

Anthracyclines and cardioprotective strategies

The incidence of AC cardiotoxicity notoriously varies in relation to the cumulative dose administered.[4] Cardinale

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et al.[5] prospectively followed a group of adult patients treated with AC for 5 years and found an incidence of cardiac toxicity of 9% and 98% of cases occurred within the first year after completion of treatment.

Cardioprotective strategies include general measures related to AC administration and specific pharmacological interventions. Measures include substitution with alternative drugs, dose reduction of AC, and special formulations, such as liposomal doxorubicin. Instead specific cardioprotective interventions, tested in randomized controlled trials (RCTs), include concomitant treatment with dexrazoxane and treatment with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) and/or beta blockers (BBs).[6] In 2006, a study on the effect of enalapril, started 1 month after the completion of high-dose chemotherapy, was conducted in a heterogeneous cohort of patients with signs of acute myocardial injury (cardiac troponin I > 70 ng/L). The primary outcome measure of cardiotoxicity, which was an absolute reduction in LVEF >10% to <50%, was not observed in any of the patients who took enalapril but in 43% of the control group.[7] Such promising data had provided the rationale for conducting other RCTs. However, the results were disappointing and reported little or no effect of using neurohormonal blockers. In the PRADA study[8] (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy), 120 patients undergoing AC therapy with or without trastuzumab were randomized to receive therapy with ARB (candesartan), BB (metoprolol), or placebo. The primary outcome was the change in LVEF from baseline to the end of adjuvant therapy, as measured by cardiac magnetic resonance (CMR) imaging. A modest decline in LVEF was observed in the candesartan group (0.8%; 95% CI, 1.9–0.4%) over 10 to 61 weeks of follow-up compared with the placebo group (2.6%; 95% CI, 3.8–1.5%). No significant change in LVEF decline was observed in the metoprolol group (1.6%; 95% CI, 2.8–0.4%) compared with the placebo group (1.8%; 95% CI, 3.0–0.7%). Analysis of circulating biomarkers showed attenuation of cardiac troponin elevation in patients receiving metoprolol, but not in those receiving candesartan, suggesting that attenuation of myocardial damage may not be reflected in changes in LVEF. Following a 2-year follow-up (PRADA EXTENDED trial), there was no significant difference in LVEF reduction measured by CMR. A reduction in LV end-diastolic volume and a minor reduction in GLS were observed in the candesartan group, while an increase in end-systolic volumes was observed in the untreated group.[9] The results of a preliminary interim analysis of a four-arm randomized study [SAFE (Cardiotoxicity Prevention in Breast Cancer Patients Treated With Anthracyclines and/or Trastuzumab)] evaluated the effect of bisoprolol, ramipril, or their combination to reduce the subclinical cardiac damage associated with AC. The 12-month follow-up results on 174 included patients demonstrated that the reduction in LVEF (assessed by three-dimensional echocardiography) was less in the ramipril and bisoprolol and ramipril groups compared with placebo. GLS worsening was also greater in the placebo group. While the study is still ongoing, the results look promising.[10]

Anti-HER2 therapies and cardioprotective strategies

Trastuzumab is a humanized monoclonal antibody that targets and inhibits HER2. The use of trastuzumab and other HER2-directed monoclonal antibodies, such as pertuzumab, has led to a marked improvement in the prognosis for women with HER2-positive breast cancer, both by prolonging survival in advanced and metastatic disease and by reducing the risk of tumour recurrence in the adjuvant setting.[2] In a recent analysis of 4207 patients treated with adjuvant trastuzumab, there was an 8.7% incidence of pauci-symptomatic or asymptomatic LV dysfunction and symptomatic heart failure in 2% of patients,[11] while population-based studies reported higher incidence rates than clinical trials; indeed in a large retrospective analysis published in 2021 by Battisti et al., the incidence of cardiotoxicity in patients treated with trastuzumab was 16.6%, and the development of symptomatic heart failure was 5.0%.[12]

The MANTICORE 101—Breast (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial evaluated the efficacy of perindopril and bisoprolol in the primary prevention of CRTD.[13] In the study, women with HER2 + early breast cancer were treated with trastuzumab; 25% of patients also received concomitant AC. No significant differences emerged between the various groups as regards the primary endpoint, i.e. the change in LV end-diastolic volume index measured by CMR.[14] However, in the secondary analyses, the decline in LVEF was attenuated by the use of bisoprolol (−1%) compared with the use of perindopril (−3%) or placebo (−5% $P = 0.001$). Furthermore, the use of perindopril and bisoprolol was associated with a much less frequent discontinuation of trastuzumab therapy compared with the placebo group. After 12 months of treatment with trastuzumab, LV end-diastolic volume increased regardless of the administration of bisoprolol, perindopril, or placebo.[11] This suggests limited ability of ACEIs or BBs to reduce LV remodelling. A subsequent trial enrolled 468 women with HER2-positive breast cancer treated with trastuzumab, including 198 previously treated with AC. The primary endpoints of the study were LV dysfunction in response to trastuzumab therapy and discontinuation of trastuzumab therapy. Participants were stratified by AC use with subsequent randomization to receive lisinopril, carvedilol, or placebo. After 12 months of treatment with trastuzumab, study participants were followed up for another 2 years. Trastuzumab treatment discontinuation (due to a reduction in LVEF) was less in patients receiving lisinopril or carvedilol compared with placebo. Overall, cardiotoxicity was comparable for the three groups, with rates of 30% for lisinopril recipients, 29% for carvedilol recipients, and 32% for placebo recipients. However, in the pre-specified analysis among patients who also received AC therapy, there was greater cardiotoxicity-free survival with lisinopril (HR, 0.53; 95% CI, 0.30-0.94; $P = 0.015$) or carvedilol (HR, 0.49; 95% CI, 0.27-0.89; $P = 0.009$) vs. placebo.[14] In this regard, it must be considered that the incidence of cardiotoxicity in this study was much higher than in most other published studies, suggesting that this was potentially a higher risk cohort and therefore the results obtained would justify the use of preventive cardioprotective therapy more in high-risk populations.

Meta-analysis

A meta-analysis published in 2019 examined the efficacy of neurohormonal drugs in preventing cardiovascular toxicity in patients undergoing chemotherapy, evaluating 17

randomized controlled trials and a total sample of 1984 patients treated with AC, HER2 antagonists, or both. Follow-up ranged from 24 weeks to 2 years. Median baseline LVEF ranged from 59 to 71% across all studies. The overall absolute attenuation of LVEF decline between patients who received prophylactic neurohormonal therapies and those who did not was only 3.96%.[15] In another recent meta-analysis, nine randomized controlled trials were included, for a total of 1362 female patients with an average age ranging from 41 to 54 years and an average duration between 63 and 365 days.[16] The peculiarity of this meta-analysis is represented by having included randomized studies exclusively conducted on patients affected by breast cancer and treatment regimens with AC, trastuzumab, or both. The primary analysis was the effect of BB and ACEI/ARB on LVEF in patients treated with trastuzumab or AC; the secondary analysis evaluated the effect of cardioprotective therapy in patients taking both trastuzumab and anthracyclines. BBs but not ACEIs/ARBs prevented LVEF decline compared with placebo, regardless of AC or trastuzumab treatment (2.4% vs. 1.5%). Compared with placebo, LVEF was significantly higher in patients assigned BB or ACEI/ARB with trastuzumab. In conclusion, BB and ACEI/ARB have been shown to attenuate the decline in LVEF during treatment with trastuzumab and anthracyclines. Intervention with BB, ACEI, and/or ARB prevented decline in LVEF compared with placebo during treatment with trastuzumab, but not with AC. BB and ACEI/ARB have been shown to attenuate LVEF decline during treatments with both antineoplastic drugs. Compared with placebo, LVEF was significantly higher in patients assigned BB or ACEI/ARB with trastuzumab but not AC. In fact, as stated in a recent editorial, a 2.3% change in LVEF is a result with little clinical implication that is not sufficient to justify the use of neurohormonal blockers. In fact, this variation would not be assessable even by CMR, a method recognized as the most sensitive in measuring LVEF with a minimum detectable variation of 5%.[17] In addition, the clinical benefit does not outweigh any side effects. In the absence of large-scale, definitive clinical outcome studies, the question of who should initiate preventive cardioprotective therapy with neurohormonal antagonists remains controversial. The results of the meta-analyses would justify the concept of initiating cardioprotective strategies based on clinical risk, rather than a universal implementation of cardioprotective treatment with BB, ACEI, or ARB in women with breast cancer.

In the field of cardioprotection, the recently published ESC guidelines[3] propose, with a class II A recommendation, the use of a regimen with ACE inhibitors or sartans and beta blockers in the primary prevention of cancer patients at high cardiovascular risk.

The use of more effective pharmacological strategies such as gliflozins or sacubitril/valsartan which is currently being investigated in the ongoing PRADA II trial [Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (NCT03760588)]cannot be excluded in the future.[18]

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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