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Prevention of chemotherapy-induced left ventricular dysfunction

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Prevention of left ventricular dysfunction predominantly induced by anthracyclines and/or trastuzumab still represents a challenge for cardio-oncology today. Indeed, this complication threatens to limit the significant gain in cancer survival achieved to date. Oncology strategies with cumulative dose limitation, continuous infusion, dexrazoxane, and liposomal formulations have been shown to decrease the risk of anthracycline cardiotoxicity. The preventive use of ace inhibitors, sartans, and/or beta-blockers has not yet provided convincing evidence and the positive effect on left ventricular ejection fraction decline appears poor without a clear clinical relevance. Assessment of the cardiovascular risk profile is a key aspect of the baseline evaluation of any patient scheduled for cancer therapy. Control and/or correction of modifiable cardiovascular risk factors is the first form of primary prevention of cardiotoxicity. It will be necessary to select populations at higher risk of developing cardiac dysfunction, identify patients genetically predisposed to develop cardiotoxicity in order to build the most appropriate strategies to correctly and timely target cardioprotective therapies.

Introduction

The improvements over the last 20 years in the early detection and pharmacological treatment of cancer have led to a dramatic increase in survival. However, this improvement in the life expectancy of cancer patients could be coupled with an increase in the risk of developing long-term chemotherapy-induced side effects. Chemotherapy-induced cardiotoxicity is a common complication of many antineoplastic therapies and a frequent cause of morbidity and mortality in cancer survivors.

Anthracyclines have been for the past five decades and are still today the key therapy in the treatment of breast and haematological cancers. However, their benefit on cancer survival is limited by cardiotoxicity, which is defined by the American Society of Echocardiography as a 10% reduction in left ventricular ejection fraction (EF) <53%.[1]

In 2017, ASCO guidelines about strategies for prevention and monitoring of ventricular dysfunction were published, which defined patients at risk as those undergoing high-dose anthracycline and/or radiation treatments, sequential anthracycline, and trastuzumab treatments, those receiving low-dose anthracyclines or trastuzumab but associated with two or more cardiovascular risk factors, patients aged ≥60 years, borderline EF (value 50–55%), previous myocardial infarction and moderate-to-severe valvulopathy.[2]

Heart failure and cardiotoxicity rates for anthracyclines reported in the literature are based on data published more than 30 years ago, with a wide range from 7% to 65%. However, little is known about the degree of EF decline caused by anthracyclines in the era of modern chemotherapy protocols. A meta-analysis by Lotrionte *et al.*[3] assessed the late incidence of anthracycline cardiotoxicity after a median of 9 years of follow-up, finding an incidence of clinically evident cardiotoxicity in 6% and subclinical

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cardiotoxicity in 18%. More recently, Cardinale et al.[4] prospectively followed adult patients treated with anthracyclines at 5 years and found an incidence of 9%. Anthracycline cardiotoxicity was detected within the first year after completion of treatment in 98% of cases.

Current clinical strategies focus on early detection of subclinical damage through cardiac imaging techniques and biomarkers; however, these interventions are focused on damage control rather than a preventive approach. Unfortunately, despite decades of research efforts to improve primary prevention strategies, there is still no satisfactory therapy to prevent this complication. Cardioprotective strategies from an oncology point of view include the use of prolonged anthracycline infusion regimens, dexrazoxane, less cardiotoxic liposomal anthracyclines, the use of intensity-modulated conformal radiotherapy, and breath control techniques. While, from the cardiology perspective primary prevention strategies have mainly focused on the use of ace inhibitors, sartans, and beta-blockers.

Clinical studies

Anthracycline

In Cardinale's study of 473 patients treated with high-dose anthracyclines, treatment with enalapril for the prevention of cardiac dysfunction was compared with placebo in 114 patients with increased troponin I levels (>0.07 ng/mL). Cardiac dysfunction was defined as a >10-point decrease in EF with values below the normal limit. Compared with control patients, patients who received enalapril showed a lower rate of cardiac dysfunction over the 12-month follow-up (0% vs. 43%, $P < 0.001$).[5]

In the PRADA[6] trial (Prevention of Cardiac Dysfunction DuringAdjuvant Breast Cancer Therapy), 120 patients with early breast cancer and no severe comorbidities undergoing adjuvant therapy with epirubicin (240-400 mg/m^2) without trastuzumab were randomized to receive an angiotensin receptor blocker (candesartan) or beta-blocker (metoprolol) or placebo and treatment was discontinued at the end of adjuvant therapy; follow-up was 10-61 weeks. The primary outcome measure was the change in EF from baseline to the end of adjuvant therapy by cardiac magnetic resonance (CMR). A modest decline in FE was observed in the candesartan arm (0.8%) compared to placebo (2.6%) ($P = 0.026$) while no significant change in FE decline was observed in the metoprolol group (1.6%) compared to those receiving placebo (1.8%). In the analysis of circulating biomarkers, attenuation of the increase in cardiac troponin was observed among patients receiving metoprolol but not those receiving candesartan, suggesting that attenuation of myocardial damage may not be reflected in changes in left ventricular function.

In the PRADA EXTENDED study,[7] conducted up to 2 years after randomization, a small decline in EF but no significant between-group differences were observed from baseline to extended follow-up. The decline in EF in the candesartan group was 1.7% and in patients not receiving candesartan 1.8% ($P = 0.91$). For patients in the metoprolol group, the decline in FE was 1.6 points and the decline was 1.9%

($P = 0.73$) in patients not receiving metoprolol. There was no significant difference in the effect of the interventions compared to the doses of epirubicin used. Treatment with candesartan during adjuvant therapy was associated with a reduction in left ventricular telediastolic volume compared to the non-candesartan group ($P = 0.021$). There was also an attenuated decline in the global longitudinal strain (GLS) ($P = 0.046$) at 2 years, while no differences were observed between the groups in the changes in cardiac troponin I and T. A number of observations emerge from this follow-up study of the PRADA trial. Adjuvant therapy with epirubicin is associated with a modest but persistent decline in EF; neurohormonal blockade during adjuvant therapy did not influence the 2-year FE decline compared to placebo; the attenuating effect of candesartan on EF reduction observed during adjuvant therapy did not persist 2 years after randomization; treatment with candesartan was associated with a reduced decline in telediastolic volumes and GLS, whereas no significant effect of metoprolol on GLS or volumes was observed, nor did the interventions significantly influence troponin levels. The most important finding of the study is that the enrolled population, relatively young, without severe comorbidities, treated with low-to-moderate doses of anthracyclines is at low risk of cardiac dysfunction and adjuvant therapy is therefore safe in these patients.

The Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity (CECCY) trial studied 192 patients with HER2-negative breast cancer treated with anthracyclines and taxanes.[8] At the 6-month follow-up, carvedilol did not protect against a 10% decline in EF in 14 treated (14.5%) vs. 13 untreated (13.5%) patients compared to placebo. The EF decline was mild in both groups (1.3 in the placebo group and 0.9 in the carvedilol group). Anthracycline therapy was associated with an increase in circulating troponins, and carvedilol resulted in a significant reduction in values ($P = 0.003$).

The OVERCOME study of 90 patients with haematological malignancies compared the difference in EF from baseline at 6 months between patients treated with perindopril and carvedilol vs. untreated patients.[9] At 6 months, EF did not change in the intervention group but decreased significantly in controls, resulting in an absolute difference of 3.1% by echocardiography ($P = 0.035$) and 3.4% ($P = 0.09$) in the 59 patients undergoing CMR.

Trastuzumab

Studies evaluating the effect of neurohormonal interventions during trastuzumab therapy have also provided unsatisfactory and conflicting results.

The MANTICORE-101 Breast study conducted in 99 HER2 positive patients (23% also on anthracyclines) showed no effect on cardiac remodelling represented by the 12-month change in telediastolic volume measured by CMR in patients treated with perindopril vs. bisoprolol vs. placebo.[10] However, there was protection against EF decline, which was a secondary endpoint.

Boekhout et al.[11] enrolled 206 patients in a randomized study involving 78 weeks of treatment with candesartan (32 mg/day) or a placebo. Trastuzumab-related declines in

EF of more than 15% or an EF decrease below the absolute value of 45% occurred in 20 participants in the candesartan group

and in 16 in the placebo group, a non-significant difference. There were 3.8% more cardiac events in the candesartan group than in the placebo group ($P = 0.58$). The 2-year cumulative incidence of cardiac events was 0.28 in the candesartan group and 0.16 in the placebo group ($P = 0.56$).

In a study by Guglin *et al.*,[12] 468 women with HER 2-positive breast cancer treated with trastuzumab, 198 pretreated with anthracyclines, were studied. The primary endpoints of the study were LVD in response to trastuzumab therapy and discontinuation of trastuzumab therapy. LVD was defined as a >10% decrease in FE or a reduction to <50%. Participants were stratified for anthracycline use with subsequent randomization to receive lisinopril, carvedilol, or placebo. After 12 months of treatment with trastuzumab, study participants were followed for an additional 2 years. Treatment discontinuation with trastuzumab was lower in patients receiving lisinopril or carvedilol compared to placebo. Overall, cardiotoxicity was comparable for the three groups, with 30% for those receiving lisinopril, 29% for those receiving carvedilol, and 32% for those on placebo. In the 1-year follow-up after the end of trastuzumab, neither lisinopril nor carvedilol treatment resulted in a difference in LVD compared to placebo, whereas in the anthracycline cohort, both interventions effectively reduced the incidence of cardiotoxicity. When the anthracycline and non-anthracycline cohorts were analysed separately, there was a higher frequency of cardiotoxicity events in patients exposed to anthracyclines (70 of 180; 38%) compared to patients not receiving anthracyclines (64 of 257; 25%; $P = 0.002$).

A recent review[13] aimed to elucidate the mean decline in EF among the cancer population in the 'placebo' groups of randomized clinical trials which investigate cardioprotective agents. The primary outcome was the change in EF from baseline to post anthracycline-based chemotherapy by transthoracic echocardiography or by CMR. Nineteen relevant studies were identified with a total of 660 patients included from the placebo arms and 85% of these patients were women. The mean age was 50.6 years. The mean dose of doxorubicin was 385 mg/m^2 adjusted for body surface area. Patients were followed up for a mean duration of 6 months in the 19 included studies. The analysis showed that in placebo groups with no cardioprotective therapy, the pooled mean difference in EF was only 5.4%, much less than previously described. This has important implications in sample size calculation estimates for future clinical trial design assessing the role of cardioprotective therapy. Cardioprotection studies performed to date may have been underpowered to detect a statistically significant difference in EF between the treatment and placebo groups. Small studies have reported a greater reduction in EF from 9% to 17% after exposure to anthracyclines without cardioprotection; however, these were performed more than 15 years ago. Historically, the sample size in cardioprotection studies has been determined using the expected incidence of heart failure or cardiotoxicity with EF considered

a dichotomous variable, where the change is greater or less than 10%, depending on the definition. However, most studies testing cardioprotective agents also assess EF as a continuous variable, so the expected magnitude of EF decline should be considered when calculating statistical power.

Meta-analysis

In a meta-analysis of 17 studies enrolling 1984 patients, a modest benefit of neurohormonal therapies in attenuating EF decline was observed, with an estimated absolute benefit of 3.96% and substantial heterogeneity.[14] These results limit the possibility of recommending the routine use of neurohormonal therapy to reduce cardiotoxicity, and the findings highlight on the one hand the heterogeneity of the included studies and potential data bias, on the other, the need for large, adequately powered randomized clinical trials to determine the efficacy and safety of cardioprotective therapies and improved clinical outcomes. A subsequent meta-analysis of 22 prospective studies, including 2302 participants receiving anthracyclines with or without trastuzumab, assessed endpoints at the end of chemotherapy, at 6 months and 1 year.[15] In the 16 studies that tested the protective effects of neurohormonal therapy at the end of chemotherapy, there was a significant difference in the mean change in FE (-2.36) in patients receiving cardioprotective drugs compared to controls ($P < 0.00001$) and the benefits were confirmed at 6 months and 1 year. However, no cardioprotective effect was observed on volumes. Heart failure as a clinical endpoint was evaluated in 11 studies and was significantly lower in the treated group than in the control ($P = 0.002$).

Conclusions

The results emerging from the published studies so far show considerable discrepancies in results and the reasons for this are many: different study populations, small sample size differences in cancer treatment regimens used, baseliner risk factors, differences in cardioprotective drugs, different endpoints, and method of measurement, as well as a variable and relatively short follow-up time. Overall, there is insufficient evidence to date that neurohormonal blockade in primary prevention provides a significant long-term clinical benefit. Future trials should be designed on the population at higher risk to develop cardiac toxicity (genetically predisposed patients or high cumulative anthracyclines dose) to test the role of a pharmacological preventive approach.

In this scenario, it is essential to assess the baseline cardiovascular risk of cancer patients by means of dedicated scores that allow early identification of those at increased risk of complications and ensure a personalized approach.

Other strategies, such as exercise-based cardiac rehabilitation during chemotherapy, should be implemented as well to prevent cardiotoxicity.[15]

The development of appropriate approaches to prevent all aspects of chemotherapy-related heart failure (EF preservation, quality of life, and overall survival), must be the

Table 1 Summary of trials mod from Brown et al. [16]

	Cancer treatment	Primary end point	n	Medication	Follow up	Results	Conclusion
Avila (CECCY) 2018	Trastuzumab	EF decline >10%	200	Carvedilolo (3.125 mg twice a day → 25 mg twice a day)	6 months	No difference from placebo (13.5% vs. 14.5%)	No benefit
Boekhout 2016	Trastuzumab	EF decline of more than 15% or a decrease below 45%	206	Candesartan (16-32 mg)	2 months	Candesartan had higher incidence of cardiac events vs. placebo (0.28 vs. 0.16 P = NS)	No benefit, possible harm
Bosch (OVERCOME) 2013	Anthracycline	Absolute change from baseline in EF by ECHO and CMR	90	Enalapril (2.5 mg twice a day → 10 mg twice a day) + Carvedilol (6.25 mg twice a day → 25 mg twice a day)	6 months	EF unchanged with enalapril and carvedilol vs. −3.1% (ECHO) and −3.4% (CMR) with placebo	Benefit
Cardinale 2006 / Guglin 2019	Anthracycline / Trastuzumab only / Trastuzumab plus anthracycline	EF decrease >10% / FE decline >10% or 5% if EF <50% by ECHO or MUGA	114 / 468	Enalapril (5-20 mg) / Lisinopril (10 mg) / Carvedilol extended release (10mg) / Lisinopril (10mg) / Carvedilol extended release (10mg)	12 months / 1-2 years / 1-2 years / 1-2 years / 1-2 years	0 vs. 43% $P < 0.001$ / No difference from placebo / No difference from placebo / HR 0.53 $P = 0.015$ / HR 0.49 $P = 0.009$	Benefit / No benefit / No benefit / Benefit / Benefit
Gulati (PRADA) 2016	Anthracycline +/− Trastuzumab	Change in EF by CMR	130	Candesartan (8-32 mg) / Metoprolol (50-100 mg)	10-61 weeks	Modest decline in EF with candesartan vs. placebo ($P = 0.025$) / No change in EF with metoprolol vs. placebo	Mild benefit / No benefit
Heck (PRADA EXTENDED) 2021	Anthracycline +/− trastuzumab	Change in EF from baseline by CMR	130	Candesartan (8-32 mg) / Metoprolol (50-100 mg)	2 years	EF decline 1.7% with candesartan vs. 1.8% with no candesartan / EF decline 1.6% with metoprolol vs. 1.9% with no metoprolol	No benefit / Small reduction in LVED and preserved GLS / No benefit
Pituskin (MANTICORE-101 BREAST) 2017	Trastuzumab (25% with anthracycline)	LV remodelling: LVEDVi CMR	94	Perindopril (2-8 mg) / Bisoprolol (2.5-10 mg)	52 weeks	Attenuated EF decline but LV remodelling not prevented / Attenuated EF decline and LV remodelling prevented	Possible benefit / Possible benefit

EF: ejection fraction; LVED: left ventricular end diastolic volume; LVEDi: left ventricular end diastolic volume index; ECHO: echocardiography; CMR: cardiac magnetic resonance; HR: hazard ratio.

final goal of future cardioncology research. This need will become even compelling with the use of new and more powerful chemotherapies. (Table 1)

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