Scientific Summary

Background

Anthracycline chemotherapy has been shown to reduce the chances of cancer recurrence and death in individuals diagnosed with breast cancer and non-Hodgkin lymphoma. Anthracyclines can also cause damage to the heart muscle, potentially leading to left ventricular systolic dysfunction and cardiac failure. As cancer survival rates improve, there is growing concern about the long-term impact of chemotherapy-related cardiac toxicity.

Previous studies have revealed that approximately 5% of patients treated with high doses of anthracycline experience cardiac failure, with the prevalence rising to 10% among those aged over 65 years. The progression from initial heart muscle injury during chemotherapy to the development of left ventricular systolic dysfunction and subsequent clinical heart failure remains poorly understood. Thankfully, the severity and incidence of cardiotoxicity have decreased with the implementation of modern chemotherapy protocols that utilize lower cumulative doses of anthracycline.

To mitigate the risk of systolic dysfunction in patients receiving anthracyclines, recent clinical trials have investigated the use of medications commonly employed in heart failure treatment. However, these studies have their limitations. Firstly, they prescribed therapy to all patients, resulting in significant over-treatment since most patients do not develop cardiotoxicity. Additionally, the medications used either targeted the renin-angiotensin system or the sympathetic nervous system (β-adrenoreceptor blocker), even though the strongest evidence supports combined therapy with these medications for the treatment of left ventricular systolic dysfunction.

With modern advancements in cancer care, lower rates of cardiotoxicity are being achieved. Consequently, future trials need to focus on interventions for patients who are at the highest risk of developing cardiotoxicity. Addressing the limitations of previous studies, the Cardiac CARE trial (EudraCT 2017-000896-99, ISRCTN24439460) aims to select patients who demonstrate the most evidence of anthracycline-induced myocardial injury and randomize them into a combination treatment of candesartan and carvedilol.

Objectives

The primary goals of the Cardiac CARE trial are twofold: first, to investigate whether high-sensitivity plasma cTnI monitoring can identify patients who are at risk of developing left ventricular systolic dysfunction after undergoing anthracycline chemotherapy, and second, to determine if cTnI-guided treatment with candesartan and carvedilol can prevent the development of left systolic ventricular dysfunction. By achieving these objectives, the findings of the Cardiac CARE trial will have immediate practical implications for clinical practice by testing a straightforward monitoring and intervention pathway that can be easily implemented within cancer treatment centers. The primary endpoint of the study was to measure the change in left ventricular ejection fraction using cardiac magnetic resonance imaging conducted six months after the final dose of anthracycline chemotherapy. The first secondary endpoint and main secondary objective were to establish the specificity of hs-cTnI monitoring for cardiotoxicity by assessing the change in left ventricular ejection fraction in the low-risk non-randomized group. Additional secondary endpoints included evaluating hs-cTnI concentrations, conducting further cardiac magnetic resonance imaging measurements to assess the efficacy of candesartan and carvedilol treatment, and determining the specificity of hs-cTnI monitoring for cardiotoxicity. The study summarized clinically relevant thresholds for grading anthracycline cardiotoxicity based on treatment, but no formal statistical testing was performed due to inadequate power and the risk of testing multiple hypotheses simultaneously.

Methods

The study was conducted in accordance with the Declaration of Helsinki and received approval from the South East Scotland Research Ethics Committee (17/ES/0071). It followed a prospective, randomized, open-

label, blinded endpoint design. All patients received standard of care and underwent cardiac magnetic resonance imaging before and six months after completing anthracycline chemotherapy. Patients with high sensitivity plasma cTnI concentrations in the upper tertile during chemotherapy were randomly assigned in a 1:1 ratio to either receive standard of care alone or standard of care along with combined candesartan and carvedilol therapy. Patients aged 18 or older who were starting anthracycline treatment for adjuvant or neo-adjuvant therapy of breast cancer or non-Hodgkin lymphoma were eligible to participate. To focus on the dose-dependent nature of anthracycline cardiotoxicity and considering the lower incidence observed in recent studies, only patients scheduled to receive a cumulative dose of at least 300 mg/m2 of epirubicin or 150 mg/m2 of doxorubicin over 3, 4, or 6 cycles of treatment were approached. In comparison, the Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) study included 60% of patients receiving low-dose anthracycline (cumulative epirubicin dose ≤240 mg/m2), and around 20% of them also received trastuzumab. Cardiac CARE excluded patients with HER-2 positive disease scheduled for trastuzumab treatment. Although studying the outcomes of patients receiving anthracycline followed by trastuzumab is clinically relevant, it would require a larger study to account for the effects of two agents with interacting but distinct mechanisms of myocardial injury and potentially reversible changes in left ventricular ejection fraction occurring over an additional 15 months of trastuzumab administration. Plasma hs-cTnI concentrations were measured before and during chemotherapy to identify patients at high risk. The thresholds for randomization were based on findings from a pilot study that identified patients with high sensitivity plasma cTnI concentrations in the upper tertile upon completion of anthracycline chemotherapy.

Patients were randomised using a web-based service to ensure allocation concealment and avoid bias. Randomisation was performed between the standard of care alone and the standard of care plus combined candesartan and carvedilol (cardioprotection) therapy groups. Patients assigned to the treatment intervention started with 8 mg of candesartan once daily, with dosage increases of at least 3 days to reach 16 mg and 32 mg once daily. Simultaneously, carvedilol was initiated at 6.25 mg twice daily and increased to 12.5 mg and 25 mg twice daily. The medications were dispensed on the day of randomisation and continued until the completion of the study or withdrawal from participation. Adherence to medication was recorded through dose titration clinics and patient diaries. Patients with plasma hs-cTnI concentrations below the randomization threshold remained on standard of care alone. Health utility, measured by the European Quality of Life Scale EQ-5D-5L questionnaire, was assessed at chemotherapy cycle 1 by a research nurse and approximately every 9 weeks until the completion of the study (a total of 5 times).

Sample size and statistical analysis

The Cardiac CARE trial aimed to enroll at least 168 patients from various regional cancer centers in the UK. It was estimated that approximately one-third of the enrolled patients (n=56) would develop high-sensitivity plasma cTnI concentrations that met the criteria for high risk based on the Cardiac CARE pilot study. We assumed that this threshold would select all patients at risk of experiencing a ≥5 percentage-point reduction in left ventricular ejection fraction, which may be associated with long-term clinical outcomes.
The randomization was set at a 1:1 ratio between the treatment arm and standard care. Treatment allocation employed dynamic randomisation, with minimization of group imbalances in prognostic factors, including age (≥65 or <65 years), baseline left ventricular ejection fraction (≥60% or <60%), and planned cumulative epirubicin equivalent dose (300 or >300 mg/m2). To detect a difference of 5 percentage points between groups (standard deviation 5) with 90% power at a significance level of P=0.05, we needed to randomise 23 patients per group. Accounting for an estimated 17% missing data, the sample size requirement increased to 28 patients per group, resulting in a total randomized trial size of 56 patients. Since one-third of enrolled patients were expected to be randomised, the total enrollment needed to be at least 168 patients. To assess the specificity of the plasma hs-cTnI assay for left ventricular systolic dysfunction in non-randomized patients, we aimed to demonstrate that there was no change in left ventricular ejection fraction percentage (with equivalence limits of ±2%). To achieve this, we needed complete paired magnetic resonance imaging scans from 68 non-randomized patients for a paired t-test with two-sided P=0.05, 90% power, and a standard deviation of differences of 5%.

Results

Between 4th October 2017 and 30 June 2021, 175 patients were enrolled. 57 (32.6%) of patients were randomised. 29 were allocated to cardioprotection with 2 patients in this group not completing final follow up MRI scan. 28 were allocated to standard care with 1 patient not completing final follow up MRI scan. Within the remaining 118 non-randomised group, 21 patients did not complete final follow up MRI scan. Twenty patients (68.9%) were adherent to cardioprotection treatment at 6 months. Two patients (6.9%) randomised to cardioprotection did not receive medication owing to illness at the time of randomisation. Adverse events were more common in cardioprotection compared to standard care groups (71.4% and 10.3% respectively). 7 (24.1%) participants stopped both cardioprotection drugs within 2 months owing to symptoms.

Mean (± SD) patient age in non-randomised, cardioprotection and standard care groups was 52.1 (±11.0), 54 (±14.1) and 53.5 (±13.3) respectively. Mean mass (± SD) was higher in the standard care group (82.5±16.7 kg) compared to cardioprotection (70.7±16.5 kg) and non-randomised groups (76.6±16.5 kg). 71.2% of patients had received a diagnosis of breast cancer. Non-Hodgkin lymphoma patients were more frequently randomised than breast cancer patients making up 43.9% of randomised and 21.2% of non-randomised groups. Cardiovascular risk markers and concomitant cardiovascular medication prescription were uncommon across all 3 groups. Hypertension and coronary disease were more common in the standard care group (14.3% and 7.1% respectively) compared to non-randomised (8.5% and 3%) and cardioprotection groups (6.9% and 0). Mean anthracycline dose was higher in the cardioprotection (469 mg/m^2) and standard care group (479 mg/m^2) compared to the non-randomised group (424 mg/m^2). Radiotherapy was more commonly prescribed in the non-randomised group (71.2%) compared to cardioprotection (57.1%) and standard care groups (53.6%). Patients randomised to cardioprotection or standard care had mean
(±SD) LVEF 6 months after completion of anthracycline chemotherapy of 65.7±6.6% and 64.9±5.9% respectively. After adjustment, the estimated mean difference in 6-month LVEF between cardioprotection and standard care groups was -0.4 percentage points (95% CI, -3.6 to 2.8; P=0.82).
We examined the per protocol primary efficacy outcome between randomised groups in a post-hoc sensitivity analyses. When only 19 cardioprotection patients who were adherent with treatment were included there was no change in the primary outcome. The estimated mean difference in the change in 6-month LVEF between cardioprotection and standard care groups was -0.7 percentage points (95% CI, -4.3 to 2.9; P=0.70).

In non-randomised patients the baseline and 6-month LVEF (±) SD were 69.3±5.7% and 66.4±6.3 respectively. The estimated mean difference was 2.9 percentage points (95% CI, 1.45 to 4.28; P =0.92). The main secondary objective of demonstrating zero '%-point change with equivalence of ± 2% was not met. Secondary analysis identified a difference between cardioprotection and standard care groups in adjusted LV end diastolic volume indexed for body surface area of 6.0 ml/m2 (95 % CI 0.6 to 11.4; P=0.03). There was no difference between groups for global longitudinal and circumferential strain, left ventricular mass and left atrial area. hs-cTnI concentrations were higher in the randomised groups.. Adjusted change in hs-cTnI concentration from baseline to 2 months in cardioprotection and standard care groups was 27.3 ± 7.4 ng/L and 28.8 ± 8.8 ng/L (estimated mean ±SE). The estimated mean difference was -1.6 ng/L (95% CI -17.6 to 14.4; P=0.85). There were no cardiovascular deaths or new atrial fibrillation recorded during the trial. One patient within the standard care treatment group developed congestive cardiac failure. This patient received heart failure treatment including candesartan and their ejection fraction recovered on the 6-month cardiac MRI scan. No patients met the criteria for asymptomatic cancer therapy related cardiac dysfunction (CTRCD) of a 10-percentage-point LVEF fall and fall to an absolute LVEF below 50%. Similarly the CTRCD criterion of greater than 15% fall in global longitudinal strain was uncommon across groups. Chronic myocardial injury, 2 months after completion of chemotherapy was not uncommon and similar in non-randomised (32.1%) and cardio-

protection (35.7%) groups. The proportion with chronic myocardial injury was higher (60%) in the standard care treatment group. Any recording of high hs-cTnI concentration was confined to randomised groups.

Conclusions

We found no evidence of cardioprotection effect with combined candesartan and carvedilol. This combination was associated with side effects and discontinuation of therapy was not uncommon. Our findings do not support the European Society Guidelines that give a class II recommendation for use of either an angiotensin blocker or B-blockers for high risk anthracycline treated patients.
Furthermore, the small decline in LVEF at 6 months in all groups together with the low levels of other cardiotoxicity measures cast doubt over whether any form of broadly administered cardio- protection therapy is required for these patients.

The recently published European Society of Cardio-Oncology Guidelines provide a class I recommendation for the use of cTn monitoring in anthracycline patients at high risk for cardiotoxicity. The CardiacCARE Trial findings raise doubt over whether this monitoring strategy is helpful when patients with both low and high risk hs-cTnI concentration profiles developed small reductions in left ventricular ejection fraction. Whereas the pathological link between cTn as a biomarker of anthracycline myocardial injury is clear we found no evidence that elevated concentrations strongly predict cardiotoxicity, inform disease management or improve care when added to current treatment pathways. Further analysis of the data will establish the correlation between hs-cTnI concentrations and change in LVEF and global longitudinal strain. We will also examine whether there is a threshold hs-cTnI concentration below which patients do not develop a decline in LVEF.

An LVEF decline of 4.3%, 6 months after chemotherapy may not have immediate clinical implications for an individual patient. Applied across a population, this magnitude of LVEF decline is likely to confer a generalised increased risk of future cardiac dysfunction and heart failure. Future research should be directed at understanding factors determining evolution of cardiac dysfunction with monitoring and longer term follow up studies.

This trial is registered as ISRCTN24439460

This project was funded by the National Institute for Health Research (NIHR) EME programme and will be submitted to Circulation for publication. See the NIHR Journals Library website for further project information.

(2385 words)