Abstract

Background:

Anthracycline-induced cardiotoxicity has a variable incidence and the development of left ventricular dysfunction is preceded by rises in plasma cardiac troponin concentrations. Beta-adrenergic receptor blocker and renin-angiotensin-system inhibitor therapies have been associated with modest cardioprotective effects in unselected patients receiving anthracycline chemotherapy.

Methods:

In a multicentre prospective randomised open label blinded endpoint trial, patients with breast cancer and non-Hodgkin lymphoma receiving anthracycline chemotherapy underwent plasma high- sensitivity cardiac troponin concentration monitoring and cardiac magnetic resonance imaging before and 6 months after anthracycline treatment. Patients at high risk of cardiotoxicity (plasma cardiac troponin I concentrations in the upper tertile during chemotherapy) were randomised to standard care plus cardioprotection (combination carvedilol and candesartan therapy) or standard care alone. The primary endpoint was 6-month change in left ventricular ejection fraction. In low- risk non-randomised patients with plasma cardiac troponin I concentrations in the lower two tertiles, we hypothesised the absence of a 6-month change in left ventricular ejection fraction (±2%).

Results:

Between October 2017 and June 2021, 175 patients (mean age 53 years; 87% female; 71% breast cancer) were recruited. Patients randomised to cardioprotection (n=29) or standard care (n=28) had mean left ventricular ejection fractions of 65.7±6.6% and 64.9±5.9% respectively at 6 months. 20 patients (68.9%) were adherent to cardioprotection therapy at 6 months. Adverse events were more commonly reported in the cardioprotection group with 71.4% of patients having at least one adverse event compared to 12.7% non-randomised and 10.3% standard care patients. After adjusting for age, pre-treatment left ventricular ejection fraction and planned anthracycline dose, the estimated mean %-point difference in 6-month left ventricular ejection fraction between cardioprotection and standard care groups was -0.4% (95% confidence interval, -3.59 to 2.85%; P=0.82). In low-risk non-randomised patients, baseline and 6-month left ventricular ejection fractions were 69.3±5.7% and 66.4±6.3% respectively: estimated mean difference, 2.9% (95% confidence interval, 1.45 to 4.28%; P = 0.92, not equivalent). The main secondary objective of demonstrating zero %-point change with equivalence of ⍰ 2% was not met.

Conclusions:

Combination candesartan and carvedilol therapy had no demonstrable cardioprotective effect in patients receiving anthracycline-based chemotherapy with high-risk on-treatment plasma cardiac troponin I concentrations. Low-risk non-randomised patients had similar modest declines in left ventricular ejection fraction suggesting the clinical utility of routine cardiac troponin monitoring remains undefined. The modest short-term declines in left ventricular ejection fraction suggest that early cardioprotection therapy has a limited role in patients receiving anthracycline-based chemotherapy.

Limitations

Treatment effect may have been influenced by several patients stopping cardioprotection treatment within 2 months of randomization. The trial was powered to detect a 5 %-point change in left ventricular ejection fraction and a small treatment effect was not excluded.

Future work

Future work should aim to understand the transition from small changes in cardiac function, 6 months after completion of anthracycline chemotherapy, to the late development of heart failure in this population.

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Registration:

This trial is registered as ISRCTN24439460

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