 

**CARDIAC TROPONIN I MONITORING IN BREAST CANCER PATIENTS RECEIVING ANTHRACYCLINEOR TRASTUZUMAB THERAPY: a pilot study**

**Chief Investigator Details**

**Dr Peter Henriksen, Consultant Cardiologist, Edinburgh Heart Centre, Western General Hospital, Edinburgh**

**Co-investigator and collaborators details**

**Dr Peter Hall, Senior Lecturer in Oncology, University of Edinburgh, Edinburgh Cancer Centre**

**Dr Ninian Lang, Consultant Cardiologist, Queen Elizabeth, University Hospital, Glasgow**

**Dr Iain Macpherson, Senior Lecturer in Oncology, Institute of Cancer Sciences, University of Glasgow**

**Professor Nick Mills, Professor of Cardiology, BHF/University of Edinburgh Centre for Cardiovascular Science**

**Heather McVicars,** **Lead Oncology Research Nurse, Edinburgh Cancer Centre**

**Protocol Author details**

**Dr Peter Henriksen, Dr Peter Hall, Dr Ninian Lang, Dr Ian MacPherson,**

**Professor Nick Mills, and Heather McVicars.**

**List of Abbreviations**

**CRF case report form**

**cTnI cardiac troponin I**

**ACEI angiotensin converting enzyme inhibitor**

**B-blocker Beta-adrenoceptor blocker/antagonist**

**NIHR National Institute for Health Research**

**EME Efficacy and Mechanism Evaluation Programme**

**ECTU Edinburgh Clinical Trials Unit**

**REDCap (Research Electronic Data Capture)**

1. **INTRODUCTION**

**1.1. Background**

Background: There were 48,788 new cases of breast cancer diagnosed in the UK in 2009. Advances in adjuvant systemic therapies including the use of anthracycline and trastuzumab have improved disease-free survival considerably. When given alone or in combination, these medications cause heart muscle injury. Many patients go on to have radiotherapy which is associated with the late development of coronary, valvular and pericardial disease. Follow up studies of breast cancer survivors demonstrate excessive cardiac events including early and late development of heart failure [1,2]. Prognosis from heart failure is poor [3]. The progression from heart muscle injury at the time of chemotherapy to development of clinical heart failure is not understood and no preventive treatments are available. Current practice relies on monitoring systolic cardiac function with serial scans to measure ejection fraction. Scans are conducted with ultrasound or radioisotope. These involve extra hospital visits and the latter requires a radiation dose which can be up to 30 mSv over a treatment course. Previous studies have used the circulating cardiac muscle injury marker Troponin I (cTnI) to detect early muscle injury before systolic function is impaired [4-6]. One study using a contemporary assay found elevated cTnI levels in 80% of patients who developed systolic dysfunction [4]. Previous and ongoing clinical trials have investigated whether administration of medications established in the treatment of heart failure can prevent systolic dysfunction in patients receiving chemotherapy. These studies are limited by 1. An aim to treat all patients resulting in massive over-treatment and 2. Using either an angiotensin converting enzyme inhibitor (ACEi) or B-blocker rather than co-prescription which has the evidence base for improving function and survival in patients with established left ventricular dysfunction [7].

We have completed an application to the NIHR EME Researcher led program and this has been accepted for board review.

**Research question and investigation plan**: We will use surveillance with cTnI blood testing in patients receiving cardiotoxic systemic therapy to identify early muscle injury enabling targeted protective treatment with ACEi and B-blocker. Our group has validated the clinical application of a high sensitivity cTnI assay. We demonstrated that this assay doubles the diagnosis of myocardial infarction in women with chest pain by defining a lower gender-specific reference range [8]. We believe it will improve detection of heart muscle injury compared to previous studies with contemporary assays. Patients recruited into the study who exhibit a cTnI level above the upper limit of normal will be randomised to receive either carvedilol and enalapril (B-blocker and ACEi) or continue with no treatment. The study will recruit 168 patients between two regional cancer centres. Patients will have cardiac function (ejection fraction) monitored with serial cardiac magnetic resonance imaging (MRI) scans. Cardiac MRI is the most precise measure of cardiac function and provides additional measures of systolic volume and cardiac strain that inform on early mechanisms of chemotherapy induced cardiac muscle injury. The endpoint will be lowest ejection fraction during chemotherapy. The hypothesis is that carvedilol and enalapril will prevent development of cardiac dysfunction in at-risk patients identified by elevated cTnI levels. Additional outcomes include treatment effect on ongoing cardiac injury (persistence of cTnI elevation), death and heart failure and a provisional health economic analysis.

**1.2. Rationale for the Study**

We have received favourable comments from the preliminary review of our outline application to NIHR. The major criticism was the lack of pilot data in our study population using the high-sensitivity cTnI assay. We have indicated in our response to the review that we are seeking approvals to take blood from breast cancer patients attending Edinburgh Cancer Centre and the Beatson Institute in Glasgow. The purpose is to provide information on changes in circulating concentration of cTnI during treatment with anthracycline and trastuzumab. This information will be crucial to inform our research study protocol.

1. **STUDY OBJECTIVES**

**2.1. Primary and Secondary Objectives**

This study will provide descriptive information of changes in cTnI concentrations using the high sensitivity assay as patients on breast cancer treatment pathways progress through cycles of anthracycline and trastuzumab treatment. We will collect clinical details including the presence of co-morbidities, chemotherapy dosing, any complications arising from chemotherapy and left ventricular ejection fraction measured by radioisotope MUGA scan or echocardiogram according to standard clinical care pathways.

For participants enrolled in Lothian, we will enter radiotherapy details into the CRF in order to calculate the cardiac radiation dose delivered.

**2.2. Primary and Secondary Endpoints**

1. To provide descriptive information on the proportion of patients exhibiting elevated circulating cTnI concentrations during sequential cycles (doses) of anthracycline, trastuzumab and following a course of radiotherapy using the gender specific upper limit of normal (16 ng/l).

2. To record the pattern of cTnI elevation prior to each anthracycline and trastuzumab cycle.

3. To record the pattern of cTnI elevation 12-72 h after each anthracycline cycle.

4. To record the pattern cTnI elevation following a complete course of radiotherapy for breast cancer.

5. To understand what proportion of patients with elevated cTnI levels during treatment have a subsequent return to normal (and the proportion exhibiting persistent elevation) during cycles of anthracycline and trastuzumab.

6. To examine the relationship between change in cTnI concentration and the following clinical data collected as part of routine clinical care:

a. Left ventricular ejection fraction.

b. Presence of hypertension, coronary artery disease and diabetes mellitus

c. Development of clinical complications during anthracycline, trastuzumab and radiotherapy treatment

7. To provide a feasibility assessment for the blood test monitoring protocol outlined above which will be used in our future research study to investigate therapeutic intervention in patients exhibiting elevation in cTnI.

8. To understand the effect of the delivered cardiac radiation dose on the post radiotherapy cTnI level.

1. **STUDY DESIGN**

Breast cancer patients attending for treatment in NHS Lothian, the Beatson West of Scotland Cancer Centre in Glasgow and Velindre Cancer Centre will be approached by the oncology medical or research nurse team and invited to participate in the study. They will be provided with a patient information leaflet explaining the study and research plan. They will be approached for consent on their subsequent visit for a cycle (treatment dose) of either anthracycline or trastuzumab. Trastuzumab patients will no longer be approached.

Consenting patients will have blood taken for cTnI measurement. Where possible the cTnI measurement will be performed as an ‘add-on’ to blood taken routinely as part of standard care by the GP surgery up to 5 days prior to chemotherapy or trastuzumab. Alternatively 5 ml of blood will be taken at the site prior to anthracycline and trastuzumab dosing. If an intravenous cannula is fitted for the patient’s treatment then the extra blood sample will be taken from the same cannula. A further blood sample will no longer be taken 12 to 72 h after drug infusion for anthracycline patients. For participants who were already enrolled this blood sample was taken by the GP surgery whenever possible.

The oncology research nurse or medical staff will complete a basic CRF following the first blood test. This will record, patient age, weight, planned treatment regime including details of whether radiotherapy is planned (dose, left or right breast). The presence of hypertension, coronary disease, diabetes mellitus, smoking status and left ventricular ejection fraction will be recorded prior to starting treatment. Blood test sampling will be repeated at every anthracycline and trastuzumab treatment cycle. At each treatment cycle a basic CRF will be completed confirming the dose of anthracycline or trastuzumab given and updating if clinical complications have occurred and the results of further measures of left ventricular ejection fraction ordered by the treating medical team.

A full course of anthracycline comprises 3-6 cycles. Example regimens include but are not limited to FEC 80 or FEC75 for 4-6 cycles or FEC 100 for 3-6 cycles. One year (18 cycles given 3 weekly) of trastuzumab is standard, although this may occasionally be given weekly. For this pilot study, patients already established on these treatments (mid-treatment) may be approached. Trastuzumab patients will no longer be approached. Some patients continue from anthracycline to trastuzumab therapy and blood test monitoring will continue according to ongoing consent. A further blood test will be taken 3 weeks after the last anthracycline or trastuzumab cycle. This will be the final blood test for patients not receiving radiotherapy. For patients proceeding to radiotherapy this blood test will be taken prior to the first dose of radiotherapy and they will provide a final blood test after the radiotherapy course has been completed.

Monitoring for treatment complications and radioisotope MUGA scans or echocardiogram with LVEF measurement by Simpson’s rule conducted to evaluate left ventricular ejection fraction will be conducted according to current clinical protocols in both centres. Patients treated in the context of other clinical trials will be eligible.

Blood tests will be performed in NHS clinical laboratories in Glasgow, Lothian and Cardiff. The high sensitivity cTnI assay is currently in use at participating sites and performance is being monitored by an independent Data Monitoring Committee in a trial lead by the applicants to evaluate the impact of high-sensitivity cardiac troponin I testing on outcomes in patients with suspected acute coronary syndrome (High-STEACS*,* UKCRN 14322). There is no additional requirement for sample preparation and we are not storing blood for later use.

**Missing data**. It is possible that patients are unable to return for the repeat blood test 24-72 h after anthracycline dosing. We will record missing data and this information (the importance of the post-drug sample) will inform design of our subsequent research study protocol. The post-anthracycline dosing blood test is no longer required.

**Elevated cTnI levels.** We expect a substantial proportion (50%) of patients to exhibit a cTnI level above the gender specific upper limit of normal (16 ng/l for women) at some point during drug treatment. Clinical monitoring for the development of cardio-toxicity using radioisotope MUGA scans will continue according to established protocols in both centres. There is no data available to inform treatment decisions in the presence of small cTnI elevations. The clinical team treating the patient will be informed if more substantial elevations in cTnI are recorded (defined as > 100 ng/l). In this setting the treating clinical team may choose to perform further cardiac imaging to assess left ventricular function.

1. **STUDY POPULATION**

**4.1. Number of participants**

We aim to recruit a minimum of 50 participants undergoing (neo-) adjuvant systemic therapy for breast cancer.

**4.2. Inclusion/exclusion criteria**

We will recruit breast cancer patients aged between 16-90 years of age.

**Anthracycline:** For the future cardioprotection intervention study, only breast cancer patients planned to receive FEC 80 (or FEC75) delivering 480 mg/m2 (480mg/m2) of epirubicin which is analogous to a minimum 300 mg/m2 doxorubicin equivalent dose will be approached. To provide information on anthracycline dose effect in this pilot study we will include patients planned to receive any neoadjuvant or adjuvant anthracycline containing chemotherapy including:

* 1-6 cycles FEC 75
* 1-6 cycles FEC 80
* 1-6 cycles FEC 100 (which may be in the context of FEC-docetaxel or FEC-paclitaxel)
* EC90 1-6 cycles

**Trastuzumab:** Breast cancer patients receiving only trastuzumab will no longer be enrolled.

**Radiotherapy:** All patients who progress to have radiotherapy will be invited to attend for a final blood sample 3 weeks after their last radiotherapy dose.

This study does not involve any treatment or intervention. There are no exclusion criteria.

* 1. **Identification of participants**

Patients attending breast cancer clinics and oncology day units for treatment will be identified by the Oncology research nurse team on site together with Drs Hall, Hale (NHS Lothian) and MacPherson (Glasgow).

* 1. **Consent**

Patients will be approached at clinic and in the oncology day unit and invited to participate in this study. Patients expressing an interest will be given a patient information leaflet. They will be approached for consent prior to their next dose of anthracycline. A member of the oncology research team or Drs Hall and MacPherson or delegated medical staff will take consent.

* 1. **Risks and Benefits to Participants**

When the study started it involved an extra episode of venepuncture and blood testing following drug treatment. This additional test involved the inconvenience of attending hospital 24-72 h after the drug infusion. Patients were offered reasonable travel expenses for this visit. This extra blood test is no longer required.

1. **DATA COLLECTION**

The eCRF database will be built and maintained by Edinburgh Clinical Trials Unit using the REDCap (Research Electronic Data Capture) software. The research nurse will enter the data into a secure online eCRF at baseline and, if applicable, following the 24-72 h blood sample after each treatment cycle. Anonymised blood cTnI levels will be taken from the established electronic reporting systems within both centres and recorded into the online database.

A clinical oncology registrar, who is on the study team, will collect detailed information about the radiotherapy dosing for the Lothian participants and will enter these data into the eCRF.

A login name and password will be required for any individual to access the eCRF.

1. **STATISTICS AND DATA ANALYSIS**

**6.1. Sample Size calculation and proposed analyses**

The principal aim of this pilot study is to provide descriptive data on the incidence of elevated cTnI concentrations in patients receiving anthracycline or trastuzumab treatment with or without radiotherapy for breast cancer. Information on the frequency and magnitude of cTnI elevation together with the pattern: sustained or episodic (occurring after drug dosing and returning to normal before the next dose in 3 weeks) will be collected. We have been asked to provide this data following review of our EME research proposal by the NIHR to use cTnI blood testing to target cardioprotection therapy in breast cancer patients.

The radiotherapy dose parameters will be collected for Lothian participants. These will be analysed to determine if there is any dose parameter or dimension that has any specific impact on cTnI levels after radiotherapy.

1. **DATA PROTECTION**

**7.1. Data Protection**

Published results will not contain any personal data that could allow identification of individual participants.

**7.2. Data Storage**

Patient data will be collected and managed using REDCap electronic data capture tools hosted at the University of Edinburgh and stored on a secure university server. Patient consent forms will be kept under secure storage in ECTU. Blood test results will be recorded on the secure online eCRF database REDCap.

* 1. **Confidentiality**

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor will be obtained for the disclosure of any said confidential information to other parties.

1. **END OF STUDY**

End of study is defined as the last participant’s last visit, unless terminated earlier by the Investigators or co-sponsors, in which case written justification will be provided for the end of the study. Study documentation will be kept for 3 years from the protocol defined end of study. Study documentation will not be destroyed without permission from the sponsor.

1. **REFERENCES**

1. Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007;**99**(5):365-75.

2. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;**97**(11):2869-79

3. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;**342**(15):1077-84

4. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;**109**(22):2749-54

5. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 2010;**28**(25):3910-6

6. Sawaya H, Sebag IA, Plana JC, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol 2011;**107**(9):1375-80

7. National Institute for Health and Care Excellence. Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. (Clinical Guideline 108). 2010. Secondary National Institute for Health and Care Excellence. Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. (Clinical Guideline 108). 2010. 2010. <http://www.nice.org.uk/guidance/cg108>.

8. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015;**350**:g7873