ISRCTN69560410 https://doi.org/10.1186/ISRCTN69560410

Cardiac damage prevention in patients undergoing chemotherapy for breast cancer using docosahexanoic acid (DHA) and carvedilol

Submission date 08/06/2016	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 04/07/2016	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 06/02/2020	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cardiotoxicity refers to a health condition where the heart muscle is damaged electrical activities of the heart (which affects the beating of the heart and heart rate) is affected. Chemotherapy treatment is one of the causes of cardiotoxicity. Chemotherapy-induced cardiotoxicity (AIC) is a major cause of death and disease in cancer survivors. Anthracyclines are the drugs mostly responsible for the condition. Compared with other more common frequent forms of cardiomyopathy (chronic disease of the heart muscle) , AIC has an especially poor prognosis. It does not respond well to treatment and some 60% of people with AIC die within two years. There is evidence to suggest that oxidative stress has an important role in the development and progression of AIC. Oxidative stress happens when there are too many free radicals in the body. Free radicals are known to cause damage in body cells. The aim of the study is to look at the potential benefit of docosahexanoic acid (DHA) in addition to carvedilol (a beta blocker) to reduce the heart damage due to anthracycline chemotherapy in patients with breast cancer.

Who can participate?
Women aged between 18-75 with breast cancer and who are about to undergo anthracycline chemotherapy for the first time.

What does the study involve?
The participants are randomly allocated to one of two groups. into one of two groups. Those in the study group are treated with a high dose of DHA along with carvedilol for a few days before their chemotherapy begins. They are then treated with lower doses of these drugs during their chemotherapy treatment. The control group undergo chemotherapy treamtne as usual but are also given placebo (dummy) pills to represent the DHA and carvedilol. Biomarkers of oxidative stress are measured and MRI imaging taken before the study begins and after it ends. All patients are given a clinical follow up on days 10, 15, 30, 84, 180 with a final follow up at 12 months.

What are the possible benefits and risks of participating?
Possible benefits include the prevention of heart problems in the patients in the study group. All participants may benefit from having the clinical follow-up. Possible risks include minor and and reversible side effects related to the drugs included in the study like gastrointestinal discomfort (stomach ache) and bradycardia (slow heart rate).

Where is the study run from?
1. San Juan de Dios Hospital (Chile)
2. Del Salvador Hospital (Chile)

When is the study starting and how long is it expected to run for?
May 2016 to June 2020

Who is funding the study?
Scientific and Technological Development Fund (Chile)

Who is the main contact?
Dr Juan Guillermo Gormaz Araya
jgormaz@med.uchile.cl

Contact information

Type(s)
Scientific

Contact name
Dr Juan Guillermo Gormaz Araya

ORCID ID
http://orcid.org/0000-0003-3424-4807

Contact details
Clínica Alemana de Santiago
Vitacura 5951
Vitacura
Santiago
Chile
7650568
+56-2-22106211
jgormaz@alemana.cl

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

11150999

Study information

Scientific Title
Pharmacological preconditioning with docosahexanoic acid (DHA) plus carvedilol to prevent cardiotoxicity associated with anthracycline chemotherapy in patients with breast cancer

Acronym
CarDHA

Study objectives
Patients with breast cancer that receive DHA and carvedilol seven days before and three months after the first cycle of doxorubicin will present at least 50% least cardiotoxicity-derived heart damage than patients that receive the same chemotherapy with double placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
University of Chile Clinical Hospital, Faculty of Medicine of the University of Chile, 28/12/2015, ref: 208-2015

Study design
Randomized double-blind placebo-controlled clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet. Contact information Dr. Rodrigo Carrasco; email: rcarrascoloza@gmail.com

Health condition(s) or problem(s) studied
Doxorubicin-induced cardiotoxicity

Interventions
The participants (female patients with breast cancer) are randomised into one of two groups:

1. The study group will be exposed for a short period to a high dose of DHA (1500 mg/day a few days before the beginning of the chemotherapy), and carvedilol (25 mg/day a few days before

the beginning of the chemotherapy), and then treated with a low dose of these drugs for the next 3 months.
2. The control group will be exposed to double placebo in similar timings.

Previous:
Biomarkers of oxidative stress will be measured and imaging taken pre and post intervention. All patients will have clinical follow up on the days 10, 15, 30, 84, 180 with a final follow up at 12 months.

Current as of 25/02/2019:
Biomarkers of oxidative stress will be measured and imaging taken pre and post intervention. All patients will have clinical follow up on the days 30, 90, 180 with a final follow up at 12 months.

Intervention Type
Drug

Drug/device/biological/vaccine name(s)
1. Docosahexanoic acid 2. Carvedilol

Primary outcome measure
1. Affected tissue and cardiac remodeling at six months, measured using cardiac magnetic resonance at baseline and 3 months after the end of chemotherapy
2. Change from baseline in global LVEF, measured using echocardiogram and cardiac magnetic resonance. Ecocardiogram is taken measure at baseline, 3 and 6 months after the end of chemotherapy, MRI at baseline and 3 months after the end of chemotherapy
3. Change from baseline in corrected QT Interval via electrocardiogram, at baseline, day 2, 4 and 3 months after the end of chemotherapy

Previous:
4. Change from baseline in NT-ProBNP, via plasmatic levels, measured at baseline, day 2, 4 and 3 months after the end of chemotherapy

Current as of 25/02/2019:
4. Change from baseline in NT-ProBNP and hs-cTnT, via plasmatic levels, measured at baseline, day 2, 4 and 3 months after the end of chemotherapy

Secondary outcome measures
1. Lipid peroxidation (Malondialdehyde levels) at baseline, day 2, day 4 and 3 months after chemotherapy
2. Erythrocyte antioxidant enzymes activity (SOD, CAT, GSH-Px) at baseline, day 2, day 4 and 3 months after chemotherapy
3. Erythrocyte Tiol Index (GSH/GSSG), at baseline, day 2, day 4 and 3 months after chemotherapy
4. Ferric reducing ability of plasma (FRAP) at baseline, day 2, day 4 and 3 months after chemotherapy

Overall study start date
30/05/2016

Completion date
30/06/2020

Eligibility

Key inclusion criteria
1. Females aged between 18 and 75 years old
2. Breast Cancer Diagnosis
3. Entering first cycle of chemotherapy
4. Performance status of 0-2 in the Eastern Cooperative Oncology Group (ECOG) score.
5. Subject must be able and willing to sign an informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
32

Key exclusion criteria
1. History of renal (serum creatinine greater than 2 mg / ml) or hepatic insufficiency (bilirubin> 3.0 mg / dl or serum albumin <3.5 g / dl or prothrombin time <60% in the absence of oral anticoagulant therapy or ultrasound signs of chronic liver damage)
2. History of heart failure
3. History of cardiac valvulopathy
4. Baseline LVEF <50% determined by transthoracic echocardiogram
5. Cardiogenic shock
6. Any serious medical co-morbidity that determine life expectancy < 6 months
7. Current participation in any other clinical investigation
8. Any condition that contraindicates chemotherapy (i.e. Pregnancy, Lactation)
9. History of severe adverse reaction to carvedilol
10. History of severe adverse reaction to DHA
11. Previous treatment with beta-blockers within the last 3 months
12. Use of Vitamin E, Vitamin C or probucol, during the last three months
13. Use of oral anticoagulants
14. History of coagulation disorders

Date of first enrolment
30/05/2016

Date of final enrolment
30/01/2020

Locations

Countries of recruitment
Chile

Study participating centre
San Juan de Dios Hospital
Huérfanos 3255
Santiago
Chile
8350488

Study participating centre
Del Salvador Hospital
Avenida Salvador 364, Providencia
Santiago
Chile
7500922

Sponsor information

Organisation
Scientific and Technological Development Fund (FONDECYT; Fondo de Desarrollo Científico y Tecnológico) (Chile)

Sponsor details
Moneda 1375
Santiago
Chile
8340486
+56-2-23654400
esilva@conicyt.cl

Sponsor type
Government

Website
http://www.conicyt.cl/fondecyt/

ROR
https://ror.org/02ap3w078

Funder(s)

Funder type
Government

Funder Name
Scientific and Technological Development Fund (FONDECYT Fondo de Desarrollo Científico y Tecnológico) (Chile)

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
30/09/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a repository. The repository used is owned by the study since the researchers requested to the San Juan de Dios Hospital an exclusive physical space with single, controlled access. Additionally, all physical records including Informed consent copies are kept in locked file cabinets inside the repository. All study information is first recorded in physical documents in exclusive folders for each patient that are then transferred to a study-specific database on two computers located on the premises with access to the network and server backup. The computers containing records are password-protected. There is no persistent weblink or public access. The datasets generated and/or analyzed during the current study will be available from the corresponding author on reasonable request. The researchers intend to keep the study records for a period of 5 to 10 years once the results are published. The study is being conducted in accordance with "Good Clinical Practice" recommendations, based on the Declaration of Helsinki (2002). Written informed consent is obtained from all patients prior to trial participation. After an initial clinical evaluation and explanation of the study protocol, patients agreeing to participate sign the informed consent. All computer and networking entries will be done using identification number only, where possible. The research team will collect, assess reports and manage the data monitoring and reported adverse events. Any data, forms, reports, results and other records will be identified only with a participant identification number to maintain confidentiality. However, the protocol will be discontinued in any patient who develops congestive heart failure or any other adverse acute cardiac effect reverting to standard care and will be unblinded.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	04/02/2020	06/02/2020	Yes	No