ISRCTN12628444 https://doi.org/10.1186/ISRCTN12628444

Development of a program for early diagnosis and treatment of heart complications caused by chemotherapy for breast cancer

Submission date
03/07/2022

Recruitment status
No longer recruiting

Registration date
21/07/2022

Overall study status
Completed

Last Edited
04/12/2023

Condition category
Circulatory System

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Chemotherapy is one of the main treatments for cancer patients, although it is associated with causing heart problems. The adverse effects of chemotherapy on the heart and blood vessels have been proven to accelerate the development of chronic heart failure and significantly limit its positive clinical effects. Even targeted anticancer treatments can lead to the development of blood clots in veins and arteries (thrombosis), circulating blood clots (thromboembolism), high blood pressure, and heart failure, especially in patients with prior cardiovascular disease. Up to 3% of breast cancer patients treated with a targeted drug called trastuzumab can expect to experience severe cardiotoxic complications, while the combined uptake of the anticancer antibiotic anthracycline and trastuzumab leads to a 7-fold increase in chronic heart failure risk. As is known, the only method to prevent unfavorable cardiovascular events is strict monitoring for symptoms as chemotherapy is administered, with follow-up after completion of treatment.

Thus, the present research aims to develop a program for early diagnosis and treatment of the heart complications of breast cancer therapy. In the first part of the study, the proportion, structure, and factors linked to the heart complications of breast cancer chemotherapy will be assessed in data from the Cancer registry 2018-2019. In the latter part of the study, the blood levels of particular biological molecules (biomarkers) that are a sign of either normal or abnormal cell functions (of damage, inflammation, neurohormonal activation, oxidative stress, fibrosis, and thrombosis) will be assessed in patients with breast cancer for their predictive value. The assessment will also look at their relationship with impaired heart functions during or after breast cancer chemotherapy. The usefulness of these markers in detecting early dysfunction of the heart will be assessed using advanced heart imaging (heart global longitudinal strain [GLS] assessment). The study's eventual goal is to select the most sensitive and cost-effective algorithm to predict early cardiotoxic complications during chemotherapy in breast cancer patients.

Who can participate?
Women of any age with a verified diagnosis of breast cancer at any clinical stage who were admitted to the Oncologic center for chemotherapy with anthracyclines or targeted therapy, and without symptoms of heart failure established within 30 days before admission

What does the study involve?
The first, retrospective stage, is just database research, and patients are not involved. Participants will be asked to join the study during the prospective stage upon admission to the hospital for chemotherapy. On signing the informed consent, all selected participants will be stratified into four large groups depending on the risk of possible cardiovascular complications. Patients will be provided with adequate cardioprotective treatment if needed. At baseline, and then in three, six, nine, and twelve months, participants will be tested by heart imaging (echocardiographical) methods (Holter monitoring, speckle tracking - ultrasound for global longitudinal strain assessment) and blood will be collected to quantify for biomarker levels of cardiac troponin (cTnI), brain natriuretic peptide (BNP), C-reactive protein (CRP), myeloperoxidase (MPO), Galectin-3 (gal-3) and D-dimer. This data collection lasts about two years in total (22 months). Participants will be asked to visit a doctor five times.

What are the possible benefits and risks of participating?
There is no immediate benefit to those taking part. But there is an advantage of being allocated in the risk group at baseline and finding out your own cardiovascular condition free of charge (speckle tracking technologies and selected biomarker analyses are not provided free of charge in the country). There are no risks in undergoing such an examination.

Where is the study run from?
West Kazakhstan Marat Ospanov Medical University (Kazakhstan)

When is the study starting and how long is it expected to run for?
August 2020 to December 2023

Who is funding the study?
Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan (Kazakhstan)

Who is the main contact?
1. Dr Saule Balmagambetova
saule.balmagambetova@zkmu.kz
2. Dr Zhenisgul Tlegenova
zhenisgul.tlegenova@zkmu.kz

Contact information

Type(s)
Principal investigator

Contact name
Dr Saule Balmagambetova

ORCID ID
https://orcid.org/0000-0003-4080-5383

Contact details
Department of Oncology
West Kazakhstan Marat Ospanov Medical University
68 Maresyev Street
Aktobe
Kazakhstan
030019
+77055794637
saule.balmagambetova@zkmu.kz

Type(s)
Scientific

Contact name
Dr Zhenisgul Tlegenova

ORCID ID
https://orcid.org/0000-0002-3707-7365

Contact details
Department of Internal Diseases-2
West Kazakhstan Marat Ospanov Medical University
68 Maresyev Street
Aktobe
Kazakhstan
030019
+77074998565
zhenisgul.tlegenova@zkmu.kz

Additional identifiers

Study information

Scientific Title
Development of a program for early diagnosis and treatment of cardiotoxic complications caused by chemotherapy for breast cancer (PREDICATE)

Acronym
PREDICATE

Study objectives
Early detection of cardiotoxic symptoms during chemotherapy is vital for cancer patients' survival and quality of life. The project aims to develop an algorithm to prevent cardiotoxic complications during chemotherapy. Among the methods used to evaluate heart activity, the assessment of global longitudinal myocardial strain (GLS) is the most effective, although it is pretty expensive. In contrast, evaluating cardiotoxicity with cardiac biomarkers would be more cost-effective. Therefore, there is a need to determine the predictive value of assessing biomarkers of cardiac cell damage, inflammation, etc., as well as assessing the GLS in chemotherapy patients. Determining the incipient stages of cardiotoxicity in breast cancer patients by detecting the earliest responding biomarkers would allow the development of a cost-

effective algorithm for the timely correction of the cardiotoxic effects of chemotherapy that would also use relatively cheap methods. Thus, the essence of the project is to find correlations between the decrease in systolic myocardial function recorded by echocardiography, including speckle tracking, and the values of the responsive biomarkers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/09/2020, West Kazakhstan Marat Ospanov Medical University's local Bioethics Committee (68 Maresyev Street, Aktobe, 030019, Kazakhstan; +7 701 710 7958; lbk_zkmu@mail.ru), ref: No. 7

Primary study design
Observational

Study design
Single-center observational mixed quasi-experimental design study

Study type(s)
Screening

Health condition(s) or problem(s) studied
Early diagnosis and prevention of chemotherapy cardiotoxic effects in breast cancer patients

Interventions
1. A retrospective analysis of medical records (of patients with breast cancer who were administered chemotherapy in the University's clinic during 2018-2019, inpatient and outpatient divisions).
2. A restricted intervention is provided during the 2nd stage of the study in a single-center prospective cohort study. Recording the timing and frequency of cardiotoxicity symptomatic and mainly asymptomatic (preclinical) variants by determining early myocardial dysfunction through echocardiographic methods (mainly assessing the global longitudinal strain) and estimating accompanied values of selected biomarkers.

The following variables are included in the data collection:
Biomarkers: cardiac troponin (cTnI); cerebral natriuretic peptide (BNP); C-reactive protein (CRP); myeloperoxidase (MPO), galectin-3 (gal-3), D-dimer.
Holter monitoring: 24-record 12-channel ECG using wearable devices; Transthoracic echocardiography and speckle tracking.
Data collection: every three months, 5 (five) patient visits.

The prospective samples will be divided into four groups of cardiotoxic risk at baseline (visit No. 0): very high risk, high risk, intermediate, and low risk. Patients from the first two groups will be provided with cardiac protection at baseline, one week before chemotherapy starts: depending on contraindications, Angiotensin-Converting Enzyme inhibitors (ACEIs), Angiotensin II Receptor Blockers (ARBs), Beta-blockers, or statins. The rest of the patients will also be provided with cardiac protection upon revealing the first signs of cardiotoxicity detected through one of the listed methods.

Intervention Type

Other

Primary outcome(s)

Current primary outcome measure as of 29/07/2022:
1. Number of patients who developed cardiotoxic complications, including subclinical dysfunction during chemotherapy measured using left ventricular ejection fraction (LVEF) monitoring (<53% or >10% decline from baseline) and global longitudinal strain (GLS) assessment (decrease >15% from baseline) at 12 months after the chemotherapy course started, through all groups at risk
2. One-year survival without cardiotoxic complications measured using LVEF monitoring and GLS assessment (as defined above) at 12 months after chemotherapy completion through all groups at risk

_____

Previous primary outcome measure:
1. Number of patients who developed cardiotoxic complications during chemotherapy measured using left ventricular ejection fraction (LVEF) monitoring (<50% or >10% decline from baseline) and global longitudinal strain (GLS) assessment (decrease >15% from baseline) at 12 months after the chemotherapy course started
2. One-year survival without cardiotoxic complications measured using LVEF monitoring and GLS assessment (as defined above) at 12 months after chemotherapy completion

Key secondary outcome(s)

Current secondary outcome measure as of 29/07/2022:
Measured using biomarker measurement units on immunoassay analyzers at 3, 6, 9, and 12 months for all below:
1. Presence of increased values of the tests during chemotherapy treatment:
1.1. Cardiac troponin (cTnI) - ≥0.3 ng/ml
1.2. Brain natriuretic peptide (BNP) - >100 pg/ml
1.3. C-reactive protein (CRP) - >5 mg/l
1.4. Antibodies to Myeloperoxidase (MPO) - >5 U/ml
1.5. Galectin-3 (gal-3) - >28.7 ng/ml
1.6. D-dimer - ≥0.5 mg/l.
2. Time trends in the biomarkers values elevation' onset applied to LVEF and GLS data.
3. The predictive value of a positive result (PPV) and the predictive value of a negative result (PVN) for all listed biomarkers
4. Frequency of all identified cardiovascular events during observation

_____

Previous secondary outcome measure:
Measured using Finecare analyzer immunofluorescence platform biomarker measurement units at 3, 6, 9, and 12 months for all below:
1. Presence of increased values of the tests during chemotherapy treatment:
1.1. Cardiac troponin (cTnI) - ≥0.3 ng/ml
1.2. Brain natriuretic peptide (BNP) - >100 pg/ml
1.3. C-reactive protein (CRP) - >5 mg/l
1.4. Antibodies to Myeloperoxidase (MPO) - >5 U/ml
1.5. Galectin-3 (gal-3) - >28.7 ng/ml
1.6. D-dimer - ≥0.5 mg/l.

2. The predictive value of a positive result (PPV) and the predictive value of a negative result (PVN) for:
2.1. Cardiac troponin (cTnI)
2.2. Brain natriuretic peptide (BNP)
2.3. C-reactive protein (CRP)
2.4. Myeloperoxidase (MPO)
2.5. Galectin-3 (gal-3)
2.6. D-dimer

Completion date
31/12/2023

Eligibility

Key inclusion criteria
1. Verified diagnosis of C50 malignant neoplasm of the breast at any stage (if eligible for chemotherapy), according to the Republican Protocol for Diagnosis and Treatment of Breast Cancer dated March 01, 2019, No. 56, upon admittance to the University's Medical Center
2. Any age
3. Out/inpatient treatment in the Medical Center
4. Targeted therapy upon the confirmed positive Her2 status and/or Anthracyclines administering
5. Simpson left ventricular ejection fraction ≥40% without symptoms of heart failure established within 30 days before admission to the chemotherapy division

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
120

Key exclusion criteria
Current participant exclusion criteria as of 29/07/2022:
1. Coronary heart disease (CHD) progression or congestive heart failure (CHF) decompensation
2. Simpson left ventricular ejection fraction ≤40%
3. Any recurrent comorbid pathology decompensation

———

Previous participant exclusion criteria:
1. Presence of recorded cardiotoxic effects of chemotherapy, regardless of the limitation period

2. Coronary heart disease (CHD) progression or congestive heart failure (CHF) decompensation in the previous six months
3. Simpson left ventricular ejection fraction ≤40%;
4. Decompensation of comorbid pathology within the previous three months:
4.1. Endocrine diseases
4.2. Diseases of the liver
4.3. Diseases of the kidneys
4.4. Diseases of the bronchopulmonary system

Date of first enrolment
01/09/2021

Date of final enrolment
31/07/2022

Locations

Countries of recruitment
Kazakhstan

Study participating centre
West Kazakhstan Marat Ospanov Medical Unversity, Medical Center
Building 8G
Zhanakonys
Aktobe
Kazakhstan
030017

Sponsor information

Organisation
Ministry of Education and Science of the Republic of Kazakhstan

ROR
https://ror.org/03pj6ge82

Funder(s)

Funder type
Government

Funder Name

Ministry of Education and Science of the Republic of Kazakhstan

Alternative Name(s)
Ministry of Education and Science, Republic of Kazakhstan

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Kazakhstan

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analyzed during the current study will be stored in a publically available OSF repository (https://osf.io/nykmw/). Type of data: relevant appendices to the study protocol, such as the patient's registration card (IRC), Informed consent, etc. These data will become available from the study registration in ISRCTN. As to the research datasets, which include patient codes, their downloading will be performed later (with the results' publication submitting date). These records will be available publicly for all interested persons. Some files will be protected from downloading (Excel datasets) but open for reasonable requests, for instance, for journal editors. The consent from participants for sharing the research data is obtained (pointed in the Informed consent). Data regarding patient details are anonymized, and patient codes are used.
The article on the results of retrospective research is also placed in the repository (https://osf.io/nykmw/).

IPD sharing plan summary
Stored in publicly available repository, Stored in non-publicly available repository, Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	patients' survival and their cardiovascular system condition	07/12/2021	10/11/2023	Yes	No
Results article	stratifying patients based on cancer treatment-related cardiovascular disease	09/05/2023	10/11/2023	Yes	No
Results article	Role of Clinical Risk Factors and B-Type Natriuretic Peptide in Assessing the Risk of Asymptomatic Cardiotoxicity in Breast Cancer Patients in Kazakhstan	28/11/2023	04/12/2023	Yes	No
Protocol article		06/11/2022	10/11/2023	Yes	No
Statistical Analysis Plan	version 1.0	29/07/2022	01/08/2022	No	No