HEpatic and CArdiac TOxicity Systems modelling.

Published: 05-11-2014
Last updated: 20-04-2024

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Ethical review	Not approved
Status	Will not start
Health condition type	Heart failures
Study type	Observational non invasive

Summary

ID

NL-OMON40984

Source
ToetsingOnline

Brief title
HeCaToS.

Condition

- Heart failures

Synonym
Cardiotoxic cardiomyopathy, heart failure.

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Cardiotoxicity.

Outcome measures

Primary outcome

Primary endpoint: development of cardiotoxicity, defined as the most recent guidelines: a reduction of LVEF >5% to LVEF <55% with symptoms of heart failure or an asymptomatic reduction of LVEF of >10% to a LVEF <55%.

Secondary outcome

Myocardial injury, hypertension, trombo embolic events (veneous trombo embolism/TIA/CVA), bradycardia and QT prolongation on ECG.

Study description

Background summary

Antineoplastic therapy is frequently complicated by the development of cardiotoxicity. This subject is of rising concern for both cardiologists and oncologists since many of these adverse effects are likely to have a significant impact on the overall prognosis and survival of cancer patients. Moreover, due to the increasing number of patients treated by conventional chemotherapy and signaling inhibitors (often in combination and at progressively higher cumulative doses), the incidence of cardiotoxicity is continuously growing. Therefore, identifying and understanding these effects is crucial to develop novel diagnostic and prognostic biomarkers, and to obtain new therapeutics for the successful management of cancer patients with cardiovascular complications.
Cardiotoxicity can range from asymptomatic subclinical abnormalities, including electrocardiographic changes and temporary LVEF decline or simply elevated blood pressure to life-threatening events such as congestive heart failure or acute coronary syndromes.It may occur during or shortly after treatment (acute; within days or weeks), or it may become evident a long period (late/chronic; year(s)) after termination of systemic cancer therapy. The actual magnitude of the problem is still unclear because only in two trials a prospective evaluation of cardiac function has been performed. In general, the incidence of cardiotoxicity is estimated to be 5-10% depending on the chemotherapeutic agent

used. Data from endomyocardial biopsies and troponin I measurements suggest that conventional chemotherapeutics, such as anthracyclines, can induce permanent myocardial cell injury*albeit by diverse mechanisms*and by cardiac remodelling. Signalling inhibitors currently in use, like human epidermal growth factor receptor 2 (HER2/erbB2) and angiogenesis inhibitors, predominantly affect cardiac metabolism and contractile proteins, leading to (transient) contractile dysfunction. Eventually, the increase of myocardial antineoplastic concentrations can induce myocyte cell death either by apoptosis or necrosis, a critical factor for long-term cardiovascular prognosis. Quantitative methods of assessing myocardial injury, such as endomyocardial biopsies or cardiac biomarkers, can therefore have a prognostic value. To date, data regarding prognosis and risk factors are contradictory and the relationship between abnormalities identified by non-invasive cardiac investigations and survival is not clear. Therefore, further investigation and evaluation of chemotherapy-related cardiac toxicities are necessary for early identification, prevention and treatment.
HecaToS is an integrative approach, involving 14 European partners in 6 different countries, to allow prediction of susceptibility to adverse off treatment effects in the heart of patients receiving chemotherapy for different clinical indications. The aim is to generate a flexible prediction system, that can make an in silico prediction of xenobiotic metabolism, toxic liabilities and threshold doses with regard to heart toxicity. This related to the idea that leading edge computational chemistry/chemoinformatics and systems biology, when assembled in properly configured and validated computational systems, can revolutionize predictive toxicology and human safety assessment. In order to reach this objective and access relevant data on human heart toxicity, cardiac biopsies from patients receiving cardiotoxic agents, either anthracyclines or other possible anti-cancer medications such as signaling inhibitors are crucial.

Study objective

Primary Objective: To study known heartfailure biomarkers (proteomics, microRNAs and metabolomics) for the detection and prognosis of cardiotoxicity in patients receiving antineoplastic therapy, and to discover predictive biomarker (values). In the future this will help in the understanding of mechanisms that may lead to new therapeutics.

Study design

The present study is a prospective (partial retrospectieve) cohort study to investigate the cardiotoxic adverse effects and outcome of patients receiving antineoplastic treatment. By taking biosamples, we also aim to fulfil an unmet medical need, for biomarkers to predict, diagnose or prognose cardiotoxicity, and unravel the mechanisms allowing future development of therapeutics to prevent/treat cardiotoxicity.

Recruitment will take place in close collaboration with the oncology and hematology department. Recruitment of patients will be divided into three groups:
- Acute patients: patients who will be receiving chemotherapy.
- Early chronic patients: patients with toxic cardiomyopathy who received chemotherapy <12 months ago.
- Late chronic patients: patients who previously received chemotherapy > 12 months ago.

A patient cohort consisting of approximately 500 patients diagnosed with breast cancer, leukemias or lymphomas and receiving cardio toxic chemotherapeutics such as: trastuzumab, epirubicin, doxorubicin, rituximab, mitoxantrone, daunorubicin, idarubicin or taxanes, will be recruited. The latter treatment regimens are expected to induce cardiotoxicity via direct toxic myocyte toxicity and through oxidative stress-induced inflammation. The expected number of positive cases of acute cardiotoxicity will be about 1-3% depending on the chemotherapeutic agent used. The expended number of positive cases of chronic cardiotoxicity will be about 5-10%. The period for inclusion of patients is estimated at 4 years. The follow-up duration is 5 years.
In Maastricht, every year approximately 200-250 patients with newly diagnosed mamma carcinoma will be curatively operated. Their 10-year survival is approximately 80%. Within this patient group, ~80 patients/year will receive adjuvant (in addition to primary breast surgery) or neoadjuvant (prior to primary breast surgery) chemotherapy. We estimate to include 50% (40 patients) every year with a total of aproximately 150 patients after a 4 year inclusion period.
Patients from the early chronic patient group are seen as a consult by the cardiology department as part of the regular health care. This patient group will consist of aproximately 50 patients, based on previous years.
We estimate to include 300 patients in the late chronic patient group after a 4 year inclusion period due to a follow-up program of patients from the haematology department. This patient population will consist of a variable group of treated malignancies (mainly Hodgkin lymphoma), which received cardiotoxic chemotherapy mainly more than 5 years ago.

Patients should meet all of the inclusion criteria and none of the exclusion criteria. All patients will be seen by an oncologist/hematologist and cardiologist at a specialized out-patient clinic for chemotherapy-induced heart disease, originated in the Maastricht University Medical Centre.

Study burden and risks

Group related:
The study population includes patients post- or during chemotherapy with different forms of cancer, especially breast cancer and haematological cancers. In almost all of these patients chemotherapeutics are given, which are known to be cardiotoxic. Different subgroups are made, based on the moment in time when

cardio toxicity occurs after chemotherapy (acute -, early chronic - and late chronic cardiac toxicity).

Risk benefit:

Endomyocardial Biopsies:
Endomyocardial biopsy (EMB) will only be performed upon routine clinical indication, when exclusion of other causes of cardiomyopathies, such as immune dysregulation, virus-mediated or storage diseases, need to be excluded (i.e. in patients with decreased LVEF <50% without evidence of coronary artery disease or primary valvular disease). EMB is the most sensitive and specific test to assess cardiotoxicity, virus presence, auto-immunity, storage diseases and metabolic disorders (such as M. Fabry).18-20 These EMBs are performed on the cardiac catheterization laboratory, in a procedure similar to cardiac catheterization. Through a sheath, a catheter called a pulmonary artery catheter that is guided into the right side of the heart, a biotome is guided into the heart where seven tissue samples approximately 2.0 to 3.0 millimeters in size will be obtained. The collected samples will be analyzed according to a standardized protocol. The obtained data will be used for both routine diagnostics and this study. The degree of myocardial injury will be assessed using electron microscopy on endomyocardial biopsies, which is considered to be the most sensitive and specific means of evaluating cardiotoxicity and permits direct assessment of the presence and extent of disease.21 Characteristic electron microscopy findings such as depletion of myofibrillary bundles, myofibrillar lysis, distortion and disruption of the Z-lines, mitochondrial disruption, and intramyocyte vacuolization will be examined.22 In addition, the cardiac biopsy samples will be analyzed for the detection of viral genomic nucleic acid sequences by PCR, inflammation by immunostainings (CD45 and CD3), and storage disease (Congo-red) providing a highly sensitive and specific method to diagnose or exclude different causes of cardiomyopathies. The procedure to obtain EMB is a very safe one, with a very low risk (<0,5 %) of peri-procedure complications21. This low risk is in concordance with the number of complications in our centre during the last three years. Most of the complications from transmural biopsies occur at the time of venous access, i.e. incidental arterial puncture or bleeding. The major complication is pericardial bleeding (literature up to 2 %, in our center 0.5 %), caused by incidental perforation of the right ventricle, requiring direct pericardial drainage only in 50 %. All complications, except perforation, are transient and have no long-term consequences.

Cardiac Magnetic Resonance:
CMR can only be made in CMR-proof patients this excludes patients who are claustrophobic, pregnant or when they have metal(implants). A previous study saw predictive differences in T1 values, which resulted in a higher chance for symptoms later on, a closer follow-up can be advised here. There are no mentionable risks of CMR and the estimated burden is low. CMR*s will only be made upon indication as mentioned below the tables.

Cardiac echography:
A Cardiac echography will be performed on different time points as shown in the table per subgroup. Each echocardiography will take place during a combined visit with physical examination.

Blood samples:
If possible the amount of blood taken for clinical investigation will be used for research purpose. If additional blood is needed, this will be drawn simultaneously with clinical blood samples to avoid extra burden to the patient. Later on in the research project, an additional sting may be needed if it is not possible to combine with regularly check-ups. There are no mentionable risks to this venous blood drawing. It*s in the benefit of the patient to find early markers of heart-failure so it can be diagnosed in an early stage.

Urine samples:
Urine collection has no risks. Patients collect urine samples in a cup provided by us. The estimated burden of this will be none. The benefit of the patient is still unsure. Hypothetically there might be proteins in urine which might have a predictive value in cardio-toxicity/ heart-failure.

Visit number and physical examination:
The number of visits is shown in the table and depends on the subgroup they*re divided in. If possible the research visits will be combined with the regularly visits.
Physical examination will be held during the visits (blood pressure measurement, auscultations of heart en lungs). There are no risks attached and the estimated burden will be low. It*s in the benefit of the patient to find early symptoms of heart-failure so it can be treated.

Questionnaire:
One questionnaire has to be filled in during different visits. It*s a short list, which may help detect asymptomatic patients with only subtle changes in the daily life. The burden is estimated low, because it does not take a lot of time. It*s in the benefit of the patient to find early symptoms of heart-failure so it can be treated

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Patients who have received trastuzumab, epirubicin, doxorubicin, mitoxantrone, daunorubicin, rituximab, idarubicin or taxane treatment for breast cancer, leukaemia*s or lymphomas.
-Age between 18 and 70 years.

Exclusion criteria

Known cardiac diseases or cardiac abnormalities in the past.

Study design

Design

Study type: Observational non invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	500
Type:	Anticipated

Ethics review

Not approved

Date:	05-11-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL48405.068.14