A PROspective, explorative cohort study to correlate CARdiac BIomarkers with late cardiac toxicity induced by radiotherapy alone or combined with anthracycline chemotherapy for hodgkin lymphoma (PROCARBI)

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Hypothesis:We hypothesize that the combination of biomarkers (e.g. NT-proBNP, ST2, GDF15, Galectin 3, hsTn) is an early predictor of cardiac toxicity from radiotherapy and chemotherapy in a population at risk of developing late cardiac toxicity...

Ethical review	Approved WMO
Status	Pending
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Observational invasive

Summary

ID

NL-OMON46393

Source
ToetsingOnline

Brief title
PROCARBI

Condition

- Cardiac disorders, signs and symptoms NEC
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Cardiotoxicity and cardiovascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Afdeling radiotherapie & cardiologie

Intervention

Keyword: cardiac biomarkers, cardiotoxicity, chemotherapy, radiotherapy

Outcome measures

Primary outcome

Main study parameter/endpoint

The main study parameter is the blood concentrations of a panel of biomarkers

of cardiac toxicity including NT-proBNP, ST2, GDF15, Galectin 3, hsTn.

The main studied endpoint is an increase in cardiac symptoms, as observed with

standard evaluation at the BETER poli and scores on the PROMs. This is the

case, if one of the following occurs:

- KCCQ: a mean difference over time of 5 points on the KCCQ Overall Summary

Scale reflects a clinically significant change in heart failure status.

- SAQ-7: A change in one of the scales of at least 10 points is the minimum

clinically relevant change.

- Anamnesis: the physician at the BETER clinic concludes a change in heart

failure related symptoms at the second visit compared to the visit of

inclusion.

Secondary outcome

Secondary study parameters/endpoints

* Changes on MRI, indicating possible early cardiac damage.

* Changes on the ECG.

* Scores on the individual PROMs (with the validated KCCQ: heart failure, with

the validated SAQ-7: coronary artery disease).

* General health status as measured with the validated EQ-5D.

* Late cardiac clinical toxicities (observed during the entire follow-up at the

BETER poli).

* Presence of deviations observed on the MRI of Visit 2 that were not present

at Visit 1

Study description

Background summary

1.1 * Cardiac morbidity in long-term Hodgkin Disease survivors

With improvement in chemotherapy and radiotherapy regimens, Hodgkin Lymphoma (HL) has become a highly curable disease with an overall relative survival at 10 years of >80%. Long-term survivors are however exposed to several severe late side effects from the therapy. This includes cardiovascular diseases, which negatively impacts the overall survival.. Both anthracycline-containing chemotherapy and radiotherapy (RT) to the mediastinum cause cardiovascular diseases (CVD), even 35 years after initial treatment.

Radiation-induced CVD include (a) coronary heart disease (CHD), (b) valvular heart disease (VHD), (c) myocardial dysfunction, (d) electrical conduction abnormalities and (e) pericardial disease. Follow-up studies of HL survivors show a 2 to 7 folds increased risk in cardiac death, mainly due to myocardial infarction (MI). This is significantly correlated with patients* age; the younger the patient at time of RT the larger is the risk. The risk of MI is also strongly correlated with the RT techniques, depending how much of dose is received by the heart, and follow-up time. Eventually, 3 to 6 folds higher Standardized Incidence Ratios (SIRs) of CHD, VHD and heart failure (HF) are observed in patients treated for HL compared to the general population.

Similarly, depending on the cumulative dose, anthracycline also leads to acute cardiomyopathy, chronic cardiac complications (especially HF) and increased cardiac mortality.

1.2 * A national BETER clinic

Because of the increased risk of adverse effects after HL treatment a nationwide BETER consortium (Better Care after HL, Evaluation of long-term Treatment Effects and screening Recommendations) was established in 2007. The goal was to improve the life expectancy and quality of life of Hodgkin Lymphoma and selected Non Hodgkin lymphoma (NHL) patients by reducing morbidity through the careful assessment and interventions on delayed side effects.

National follow-up guidelines for lymphomas survivors have been developed recommending this follow-up. As a result, patients previously treated at Erasmus MC were identified and since November 1st, 2015, a BETER-clinic was started at Erasmus MC to follow-up lymphoma survivors. The national cardiovascular screening guideline currently includes tests focusing on early detection of heart failure, including a physical examination, ECG, blood test to measure NT-proBNP and other risk factors of CHD, and a cardiac ultrasound every 5 years.

1.3 * Prognostic markers of congestive heart failure

The diagnosis of heart failure is often only possible when symptoms have become manifest. A panel of cardiac biomarkers (such as NT-proBNP, ST2, GDF15, Galectin 3, hsTn) could have the potential to monitor subtle changes in the heart that reflect and possibly predict adverse changes before they become clinically apparent. NT-proBNP has been established as a good marker of chemotherapy-induced damages, however for the radiotherapy it has not been formally demonstrated if a specific or a panel of markers could help early diagnosis or prognosis of heart failure.

The other markers proposed in this study, namely ST2, GDF15, Galectin 3, and hsTn, are not part of the current guideline, however they are focusing on the mechanisms of cardiac injury of the 7 physiopathological pathway of cardiac insufficiency described by Braunwald (myocardial stretch, collagene matrix remodelling, myocyte injury), excepted those involved in the renal consequences of cardiac insufficiency (oxidative stress, inflammation, neurohumoral activation, renal dysfunction) since those may only occur at a late stage (ref

Study objective

Hypothesis:
We hypothesize that the combination of biomarkers (e.g. NT-proBNP, ST2, GDF15, Galectin 3, hsTn) is an early predictor of cardiac toxicity from radiotherapy and chemotherapy in a population at risk of developing late cardiac toxicity after previous radiotherapy alone or combined with chemotherapy. We also hypothesize that imaging tests including functional US and cardiac MRI can objectively confirm those early signs of cardiac toxicities, and that the clinical impact can be assessed using PROMs.

Objectives
* Primary Objective

The primary objective is to evaluate in terms of sensitivity, specificity and predictive value a panel of cardiac biomarkers for the early detection of an increase in cardiac symptoms for HL and (selected) NHL long-term survivors. The panel of biomarkers will be compared to an evaluation including clinical assessment, ECG, heart US and PROMs.

* Secondary Objectives

* To describe the early symptoms of long-term cardiac toxicity induced by radiotherapy with or without chemotherapy for HL and NHL patients.
* Develop a screening tool for the early detection of cardiac toxicity including biomarkers, imaging tests and PROMs.
* Difference in score of Kansas City Cardiomyopathy Questionnaire (KCCQ-12) and the Seattle Angina Questionnaire (SAQ-7).
* To evaluate the value of cardiac MRI as an objective diagnostic tool for mediastinal radiotherapy and/or chemotherapy induced cardiac toxicities.
* To evaluate the dose effect relationship between the detected increase in cardiac symptoms and various late severe cardiac toxicities.
- Evaluation of the radiation with/without anthracycline dose effect relationship, and the impact of other factors of risk (age at treatment, gender, body mass index (BMI), hypertension, diabetes, dyslipidaemia, and tobacco use).

Study design

This study is a prospective explorative cohort study for patients in long-term follow-up after radiotherapy alone or combined with chemotherapy for Hodgkin and selected non-Hodgkin lymphoma to assess the correlation between a panel of blood biomarkers, cardiac US and MRI imaging, and PROMs.

Study burden and risks

This is a non-interventional prospective follow-up cohort. The burden and the risks associated with participation for the patient include those associated with blood sampling (temporary bruising and pain), imaging (time commitment and anxiety associated with going to the Hospital) and questionnaires (time and possible anxiety). With MRI contrast dye is given intravenously. This can result in hematoma and in a rare case to an allergic reaction.
Patients will be blinded to the results since the diagnostic value of the combined cardiac biomarkers, imaging test or PROMs assessment performed in this trial has not been validated. The results will be used for research purposes only. However, if the study is positive it is possible that some patients may benefit from an earlier detection of cardiovascular disease. Those patients

will then be called back and proposed standard intervention for early stage of cardiovascular disease.

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

To be eligible participating in this study, patients must meet all the following criteria:
* Previous history of Hodgkin or mediastinal non-Hodgkin lymphoma treated with mediastinal radiotherapy with or without anthracycline-containing chemotherapy
* Planned visit at the BETER clinic
* Written informed consent
* Age >< = 18 years
* With a minimum of 5 years of disease free survival

Exclusion criteria

4.3 * Exclusion criteria;Not currently under treatment for malignant disease (unless basal cell carcinoma)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2017
Enrollment:	200
Type:	Anticipated

Ethics review

Approved WMO

Date:	16-11-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	30-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL62506.078.17