Cardiomyopathy and heart failure risk after treatment for Hodgkin lymphoma or aggressive B cell non-Hodgkin lymphoma

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To assess risk factors for cardiomyopathy and heart failure among lymphoma (HL and aggressive B-cell NHL) survivors, focusing on the independent and joint effects of doses of anthracycline-containing chemotherapy (doxorubicin) and rituximab as well...

Ethical review	Approved WMO
Status	Pending
Health condition type	Lymphomas NEC
Study type	Observational invasive

Summary

ID

NL-OMON50135

Source
ToetsingOnline

Brief title
CRYSTAL case-control

Condition

- Lymphomas NEC
- Heart failures

Synonym
cardiomyopathy, Heartfailure

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Collectensfonds KWF;grantnummer 10424

Intervention

Keyword: Cardiovascular disease, Hodgkin lymphoma, Late treatment effects, non-Hodgkin lymphoma

Outcome measures

Primary outcome

Cardiomyopathy and congestive heart failure will be graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Treatment histories of cases and controls will be compared using conditional logistic regression models. We will specifically focus on exposure distributions, cumulative drug dose for each cytostatic drug used (specifically doxorubicin, cyclophosphamide and rituximab) and mediastinal irradiation. The effect of cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes mellitus type II, smoking and family history of cardiovascular diseases will also be evaluated. Radiation charts and simulation radiographs will be used to estimate mean heart dose (MHD) and the radiation dose-response relationship will be modelled. Blood samples will be used for examination of susceptibility genes for anthracycline and/or radiation induced CVDs.

Secondary outcome

Not applicable

Study description

Background summary

Over the past decades, the 5- and 10-year survival of especially patients with aggressive B-cell non-Hodgkin lymphoma (NHL) and to a lesser extent of patients with Hodgkin lymphoma (HL) has improved. There is increasing evidence that late

cardiovascular complications of cancer treatment cause substantial excess morbidity and mortality in long-term lymphoma survivors. In HL survivors, it has been found that treatment with anthracyclines and exposure of the heart to radiation are important risk factors for the development of heart failure. However, variation in anthracycline dose in previous studies among HL survivors was limited and the majority of included patients had received mediastinal radiotherapy as part of the lymphoma treatment, therefore researchers were unable to reliably assess the dose-response relationship of anthracyclines with heart failure and had limited ability to study the presence of effect modification between anthracycline exposure and exposure of the heart to radiation. In order to better quantify the individual effects of (mediastinal) radiation and anthracycline exposure, we will therefore conduct a case-control study in a combined multicentre cohort of HL and aggressive B-cell NHL survivors. Combining these two lymphoma cohorts will provide a much broader range in both anthracycline-dose and radiation exposure. Also, little is known about the possible interaction between treatment (radiotherapy and/or chemotherapy) and conventional cardiovascular risk factors or genetic risk factors and the risk of cardiomyopathy and/or heart failure. It is important to know which lymphoma survivors have an increased risk of treatment-related late effects in order to provide more targeted screening advice, medical interventions and ultimately prevention.

Study objective

To assess risk factors for cardiomyopathy and heart failure among lymphoma (HL and aggressive B-cell NHL) survivors, focusing on the independent and joint effects of doses of anthracycline-containing chemotherapy (doxorubicin) and rituximab as well as radiation dose to the heart. We will also assess whether conventional risk factors for cardiovascular diseases (CVDs), lifestyle and genetic risk factors modify treatment-related cardiomyopathy and heart failure risk.

Study design

We will conduct a case-control study that includes survivors who are already included in a cohort of Hodgkin lymphoma survivors (P11CHT study), treated between 1965 and 2000. In addition, survivors from a multicenter cohort of aggressive B-cell NHL survivors (CRYSTAL cohort study), treated between 1989 and 2012, will be included. Cases are defined as lymphoma survivors who have developed cardiomyopathy and/or heart failure after lymphoma treatment. Cases are matched to lymphoma survivors (1:3) who have not developed cardiomyopathy or heart failure, myocardial infarction or heart valve disease (controls).
Cases will be identified based on data from medical records or information from general practitioners collected in the context of the P11CHT study or the CRYSTAL control study.

We will perform linkage with the *Basis Registratie Personen (BRP)* to determine if a survivor is still alive at the start of the study and to obtain contact information. All 5-year survivors eligible as case or control who are still alive at the start of the study will be approached in writing for study participation by the survivors* former attending medical specialist, his/her successor or the head of the department where the survivor was treated. Eligible survivors will receive an invitation to participate in the study together with a reply and informed consent form and an information file. The General Data Protection Regulation (GDPR) and the Data Protection Act no longer apply to identifiable data that relates to a person once they have died, therefore, in case a HL or aggressive B cell NHL survivors eligible for inclusion has died before study start, we will assume the survivor consents to study participation. For cases and controls that are no longer alive at the time of the study, only coded data from medical files will be used in this study. For all cases and controls, detailed treatment information, including radiation charts and simulation films and cumulative doses of all cytotoxic drugs, information about risk factors for cardiovascular disease, family history and demographic data will be abstracted from medical records. In order to provide detailed radiation dose descriptions for exposure to the heart, we will also collect scanned copies of original radiotherapy prescription sheets, simulation films and radiation charts if available. For the current study, radiation dosimetry will be carried out at the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) of the University of Oxford, United Kingdom (Dr. D. Cutter and Prof. S. Darby) in close collaboration with the NKI-AVL radiotherapy department (Dr. B.M.P. Aleman).

To obtain more complete information on cardiovascular disease risk factors, survivors who are currently alive will receive a risk factor questionnaire that will elicit information on family history of cardiovascular diseases, history of smoking, alcohol use, lifetime weight changes, lifetime physical activity, premature menopause in women and medication use. The risk factor questionnaire will be sent after the participant has given consent for study participation. If the participant has given consent to donating a blood sample for examination of susceptibility genes (Genome screen array [GSA]) for chemotherapy and/or radiotherapy-induced CVDs, we will send a blood sampling package to donate a 10 ml blood sample. After gene-analysis and when the participant has consented to biobanking, the collected blood samples will be stored for future research in the biobank.

Study burden and risks

The risk and burden of the measurements for the CRYSTAL case-control study are estimated to be very low: we ask participants to complete one questionnaire and ask for one blood sample (10 ml, minimally invasive).

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

All lymphoma survivors who meet the inclusion criteria of the P11CHT study or the CRYSTAL cohort study are eligible for the CRYSTAL case-control study. The most important inclusion criteria for the P11CHT and CRYSTAL cohort study are:
* Diagnosis of Hodgkin's lymphoma (P11CHT) or aggressive B-cell non-Hodgkin's lymphoma (CRYSTAL cohort)
* Treatment for the lymphoma between 1965 and 2005 (P11CHT) or between 1989 and 2012 (CRYSTAL cohort)
* Age at diagnosis <51 years (P11CHT) or <61 years (CRYSTAL cohort)
* Still alive at least 5 years after primary lymphoma treatment

Exclusion criteria

* A history of (symptomatic) myocardial infarction, valvular heart disease, cardiomyopathy or heart failure before lymphoma diagnosis
* Chemotherapy or immunotherapy for a primary malignancy before lymphoma diagnosis
* Radiotherapy to the trunk before lymphoma diagnosis
* Myocardial infarction or *CTCAE grade 2 valvular heart disease prior to diagnosis of cardiomyopathy or heart failure
* Insufficient understanding of the Dutch language (for survivors receiving the questionnaire)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-01-2020
Enrollment:	800
Type:	Anticipated

Ethics review

Approved WMO

Date:	16-01-2020
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC NedMec

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	NL68724.031.19