Investigating cardiovascular adverse events related to cancer treatment: a study of extreme toxicity using induced pluripotent stem cells

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To identify the pathophysiology and predictors of study (extreme) cancer treatment -induced cardiovascular toxicity in cancer patients, by in vitro investigation of cardiovascular toxicity in patient-derived cardiomyocytes (iPSC-CMs) and endothelial...

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

Summary

ID

NL-OMON44465

Source
ToetsingOnline

Brief title
InvestiCAT-iPSC

Condition

- Cardiac disorders, signs and symptoms NEC
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cardiovascular adverse events after cancer treatment

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cancer treatment, cardiovascular, pluripotent stem cells, toxicity

Outcome measures

Primary outcome

The primary endpoint will be a comparison in iPSC-CM/iPSC-EC morphology, function and molecular profile (RNA sequencing, proteomic profiling) before and after exposure to anthracyclines, trastuzumab, cisplatin, bleomycin and radiation in iPSC derived from the highly susceptible groups and the highly resilient control groups.

Secondary outcome

n.a.

Study description

Background summary

Cisplatin, anthracyclines, bleomycin and trastuzumab are commonly used cytotoxic agents. Anthracyclines and trastuzumab can cause cardiotoxicity, ranging from transiently decreased cardiac function to (rarely) severe heart failure or death. During treatment with cisplatin or bleomycin, some patients experience severe cardiovascular toxicity such as myocardial infarction, stroke and severe pulmonary dysfunction. Why some patients are susceptible to extreme cardiovascular toxicity of cancer treatment is largely unknown. Unraveling extreme cardiovascular toxic responses in cancer patients may help understand the pathophysiology of cardiovascular toxicity of these agents and help in understanding the more subtle, long-term cardiovascular side effects that affect a larger part of cancer survivors. Induced pluripotent stem cells are an innovative, minimally invasive way of obtaining patient-derived cardiomyocytes and endothelial cells. With these patient-derived cells, we can recapitulate

and mimic and study pathological cardiovascular responses and cardiovascular toxicity in vitro.

Study objective

To identify the pathophysiology and predictors of study (extreme) cancer treatment -induced cardiovascular toxicity in cancer patients, by in vitro investigation of cardiovascular toxicity in patient-derived cardiomyocytes (iPSC-CMs) and endothelial cells (iPSC-ECs) using an innovative, minimally invasive way of obtaining patient-specific induced pluripotent stem cells (iPSCs).

Study design

Explorative, cross-sectional, non-therapeutic, case-control study.

Study burden and risks

The study visit will consist of physical examination, electrocardiogram, venipuncture (80 ml), urine sample, echocardiography, cMRI (optional), carotid and femoral ultrasound, and measurement of skin autofluorescence. To be able to generate iPSCs from fibroblasts, a skin punch biopsy under local anesthesia will be performed.

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

1. any proven cancer treated with curative intent;
2. age >= 18 and <= 50 years;
3. able to comply with the protocol;
4. signed written informed consent.
Furthermore, there are specific inclusion criteria for every subject group:
[A-TOX]: severe cardiovascular toxicity* during 1 to 3 cycles of anthracyclines (i.e. 60 to 180 mg/m2 doxorubicin or 90 to 270 mg/m2 epirubicin);
[A-NO]: >= 3 months after end of cancer treatment which included the maximum tolerable dose of anthracyclines (i.e. 450 to 500 mg/m2 doxorubicin or 850 to 900 mg/m2 epirucibin);
[T-TOX]: severe cardiovascular toxicity* within 1 to 6 cycles of trastuzumab (6 mg/kg/3wks or equivalent);
[T-NO]: >= 3 months after end of cancer treatment which included a year of trastuzumab (18 cycles of 6 mg/kg/3wks or equivalent).
[C-TOX]: severe cardiovascular toxicity* during 1 to 3 cycles of cisplatin (i.e. 100 to 300 mg/m2);
[C-NO]: >= 1 year after end of cancer treatment which included high-dose cisplatin (i.e. a cumulative dose of 400 to 1000 mg/m2);
[B-TOX]: severe cardiovascular toxicity* during 1 to 3 cycles of bleomycin (i.e. 90 to 270 USP);
[B-NO]: >= 1 year after end of cancer treatment which included high-dose bleomycin (i.e. a cumulative dose >= 360 USP);;* Severe cardiovascular toxicity is defined as any of grade 3 - 4 toxicity according to CTCAE 4.03, including but not limited to:
* - in the category *Cardiac disorders*:
o acute coronary syndrome (symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable - or more severe);
o cardiac arrest;
o heart failure (severe with symptoms at rest or with minimal activity or exertion; intervention indicated - or more severe)
o left ventricular systolic dysfunction (symptomatic due to drop in ejection fraction responsive to intervention - or more severe);
o myocardial infarction (severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction - or more severe);

o restrictive cardiomyopathy (symptomatic heart failure or other cardiac symptoms, responsive to intervention - or more severe);
o right ventricular dysfunction (severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated - or more severe);
* - in the category *Nervous system disorders*:
o stroke (severe neurologic deficit - or more severe);
* - in the category *Vascular disorders*:
o peripheral ischemia (recurring or prolonged (>= 24 hours) and/or invasive intervention indicated - or more severe);
o thromboembolic event (thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated - or more severe);
* - in the category *Respiratory, thoracic and mediastinal disorders*:
o pneumonitis (severe symptoms; limiting self-care ADL; oxygen indicated - or more severe);
o pulmonary fibrosis (severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis > 50 - 75% - or more severe);
* - in the category *Renal and urinary disorders*:
o acute kidney injury (creatinine > 3 x baseline or > 4.0 mg/dL; hospitalization indicated - or more severe);
o chronic kidney disease (estimated Glomerular Filtration Rate or creatinine clearance 29 - 15 ml/min/1.73 m2 - or more severe).

Exclusion criteria

1. history of cardiovascular disease prior to start of cancer treatment, as evidenced by any of the following:
a. symptomatic or treated cardiovascular disease prior to start of cancer treatment;
b. LVEF < 55% at any performed MUGA scan or echocardiography prior to start of cancer treatment;
2. any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol, or insufficient understanding of the Dutch language;
3. any contraindication for skin biopsy, including:
a. extensive skin disorder precluding biopsy of unaffected skin;
b. known allergy to local anesthetics;
4. use of anticoagulants and INR > 3;
5. pregnant or lactating female.
Furthermore, there are specific exclusion criteria for the *resilient* subject groups [A-NO], [T-NO], [C-NO], and [B-NO]:
6. history of cardiovascular disease during or after cancer treatment, as evidenced by any of the following:
a. any symptomatic or treated cardiovascular disease;
b. LVEF < 55% at any performed MUGA scan or echocardiography.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-12-2017
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO

Date:	11-10-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL62372.042.17
Other	volgt