Late effects of chemotherapy on brain functioning in the elderly

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Cytotoxic treatment may lead to long-lasting brain damage that can result in persistent cognitive changes and accelerated cognitive decline at an older age. The proposed study will investigate whether chemotherapy causes brain changes different from...

Ethical review	Approved WMO
Status	Pending
Health condition type	Structural brain disorders
Study type	Observational invasive

Summary

ID

NL-OMON31638

Source
ToetsingOnline

Brief title
Chemotherapy and brain functioning in the elderly

Condition

- Structural brain disorders
- Cognitive and attention disorders and disturbances

Synonym
cognitive deficits, memory and concentration problems

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: breast cancer, chemotherapy, cognitive decline, dementia

Outcome measures

Primary outcome

MRI measures (1.5 Tesla):

-2D proton density weighted (PDW) scan: 90 slices/1.6 mm

-FLAIR scan: 64 slices/2.5 mm

-3D T1W scan:100 slices/1.6 mm

-3D T2*W (Susceptibility Weighted SWI) scan:100 slices/1.6 mm

-2D Phase Contrast Flow Measurement

-Diffusion tensor imaging (25 diffusion tensor directions):39 slices/3.5mm

These measures will be used to assess total and regional grey matter, white matter and CSF volume and presence and severity of vascular lesions (white matter lesions, lacunar infarcts, microbleeds).

Neuropsychological measures:

Mini-Mental State examination

the Stroop test

the Letter digit substitution task

verbal fluency task

15 word verbal learning test

These tests will be used to assess impairments in verbal skills, executive

functions, attention and memory.

Secondary outcome

Age

Educational status

Smoking habits

Alcohol intake

Body mass index

Bloodpressure

Blood glucose level

Activity of hart muscle

Condition of coronary arteries

Known genetic riskfactors for cognitive decline/dementia

Age of menopause

Type of menopause (natural or artificial)

Use of hormone replacement therapy

Depressed mood

Self-reported cognitive problems

Self-reported medical history and medication use

Number of CMF cycles

Radiotherapy yes/no

Endocrine therapy yes/no

Study description

Background summary

Cancer patients who have been treated with chemotherapy frequently report cognitive complaints that they consider to result from the therapy. These cognitive complaints are of great concern to patients, and are a frequent topic in cancer support groups where they are referred to as *chemobrain*. Over the last few years, several neuropsychological studies indeed reported cognitive impairment in series of cancer patients treated with adjuvant chemotherapy. Moreover, several neurophysiological studies found abnormalities in brain functioning up to five years after cessation of treatment with chemotherapeutics and suggest that the cognitive problems in these patients may not be transient. Furthermore, animal studies showed long lasting dose-dependent decreases in cell proliferation in the hippocampal formation in rats following single intravenous administration of methotrexate, one of the frequently used cytotoxic agents. We hypothesize that also in humans cytotoxic treatment may lead to long-lasting brain damage that can result in persistent cognitive changes and accelerated cognitive decline at an older age. The proposed study will investigate whether chemotherapy causes brain changes different from the normal age related brain changes and increases the risk of worse cognitive function and cognitive decline.
We will compare brain structure and cognitive function between hundred-and-twenty women who are now aged 60 years or over and who were treated with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy for breast cancer 5 to 20 years ago, with controls without a history of cytotoxic treatment. Patients will be recruited from the Daniel de Hoed Cancer Clinic and the Antoni van Leeuwenhoek Hospital. Patients will be compared to participants of the Rotterdam Study without a history of cytotoxic treatment. The Rotterdam Study is a large on-going population based cohort study among persons aged 45 years and over living in Ommoord, Rotterdam. The standard examination protocol in the Rotterdam Study includes a neuropsychological test battery to assess cognitive function, and brain MRI scanning to assess total and regional volumes of grey matter, white matter, and CSF and presence and severity of vascular lesions (white matter lesions, lacunar infarcts, microbleeds). The cancer patients will be assessed in exactly the same way as the control subjects following the protocol of the Rotterdam Study. MRI scanning and the neuropsychological testing will take place at the research centre of the Rotterdam Study in Ommoord, Rotterdam.
This study will give insight in the long term effects of chemotherapy on cognitive function in elderly women. Furthermore, by comparing specific brain structures and brain lesions between women with and without previous chemotherapy, this study may help elucidate the mechanisms that underlie the deficits found in a number of patients treated with adjuvant chemotherapy. As CMF chemotherapy has been the adjuvant regimen of choice for more than 20 years world wide, very large number of survivors might be at risk for neurocognitive late effects of treatment. In addition, this study can be regarded as a model for the investigation of other frequently used cytotoxic regimens. It is

expected that in 2015 the incidence of breast cancer will be around 17.000 in the Netherlands alone, and that in half of these patients chemotherapy will be part of the treatment strategy. Therefore, it is important to systematically investigate any potential late effect of chemotherapy that can seriously affect the quality of the survival of these patients.

Study objective

Cytotoxic treatment may lead to long-lasting brain damage that can result in persistent cognitive changes and accelerated cognitive decline at an older age. The proposed study will investigate whether chemotherapy causes brain changes different from the normal, age-related brain changes and increases the risk of worse cognitive function and cognitive decline.

Study design

Observational study, cross-sectional

Study burden and risks

Patients will be tested once. Each test assessment will last 2.5 hour and consists of a semi-structured interview, a medical assessment in which weight, length and bloodpressure will be measured. In addition, blood will be collected and an ECG and ultrasound of coronary arteries will be performed; several questionnaires and tests and an MRI scanning session.

The patient has to lie still in the scanner which is sometimes considered inconvenient. Moreover, the scanner produces noise, which is effectively reduced by the use of earplugs and headphones. When standard safety rules are applied (no ferromagnetic objects inside the scanner room) no risks exist for the patient. The addition medical examination are not harmful. Ample experience with patient populations and with participants of the Rotterdam (ERGO study) have indicated that this procedure is feasible and is not considered too burdensome.

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

female
sufficient proficiency in Dutch language
treatment with adjuvant CMF chemotherapy for breast cancer five to twenty years ago
over 60 years old

Exclusion criteria

relapse and/or metastases
conditions that preclude MRI examination

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	120
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	NL18761.031.07