Nature and mechanism of cognitive deficits following chemotherapy: an (f)MRI study

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In our own recent studies we found indications of the existence of particular executive functioning deficits as well as memory impairments following different regimens of cytotoxic agents. Together with the indication from our animal study of a...

Ethical review	Approved WMO
Status	Pending
Health condition type	Cognitive and attention disorders and disturbances
Study type	Observational non invasive

Summary

ID

NL-OMON31092

Source
ToetsingOnline

Brief title
chemotherapy, cognition and (f)MRI

Condition

- 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: de studie wordt door het NKI gefinancierd

Intervention

Keyword: chemotherapy, cognition, MRI

Outcome measures

Primary outcome

MR scanning will be performed using a Philips Intera 3.0 Tesla scanner with an eight channel Sense head coil.

MRI imaging parameters:

1. 3-dimensional T1-weighted sequences followed by (automated) volumetric measurement, as a gross marker for tissue loss.

2. FLAIR sequence to determine presence and extent of demyelation.

3. MR Spectroscopy allows the safe in vivo measurement of brain neurochemistry. Compounds that can be identified are N-acetylaspartate (NAA), choline (Cho) and myo-inositol (MI). NAA is contained almost exclusively within neurons and is considered a neuronal marker for neuronal density and viability. MI reflects glial content.

4. Diffusion Tensor Imaging (DTI) will be used to study the (density of) fibers subserving well-defined functional networks and as such provide an index of damage in the normal appearing white matter. The outcome measures will be used to study correlations with specific functional deficits.

5. Functional MRI: EPI sequence, 35 slices/3.0 mm, TR * 2.0 s, axial sequential acquisition: We will use the following well-studied paradigms measuring executive functioning and memory to investigate changes in the blood oxygen level dependent (BOLD) response, reflecting neural activity. Tower of London Task: A task widely used to investigate executive/planning processes and known

to robustly activate dorsolateral prefrontal cortex. The Flanker task (20): Previous studies from our group consistently show impaired performance on this task by patients treated with chemotherapy. It provides a means for examining interference control processes. Activation of the anterior cingulate cortex (viewed as a central component of the neural circuit for action monitoring) is reliably observed during this task. Paired associates task, measured both at encoding and retrieval. This memory paradigm has demonstrated to reliably activate medial temporal lobe (e.g., hippocampus).

Secondary outcome

In addition to the tests that are administrated while MRI scans are being acquired, the patients will also be tested with a neuropsychological examination after the scanning procedure. This examination will consist of the following classical neuropsychological tests, that were also included in the previous neuropsychological examinations conducted at the NKI-AvL: California Verbal Learning test, Stroop color-word naming, Trail making, Verbal Fluency, Digit symbol (WAIS), Wechsler memory scale (visual memory). These tests are included to obtain information on the current cognitive status of the participants.

The following data will be collected for all participants: Age, educational status, smoking habits, alcohol intake, body mass index, age at menopause (if appropriate) and type of menopause (natural or artificial), use of hormone replacement therapy, psychological distress, self-reported cognitive problems, self-reported medical history and medication use.

For the breast cancer patients previously treated with chemotherapy the

following additional information will be obtained through the medical records:

kind of cytotoxic treatment, radiotherapy yes/no, endocrine therapy yes/no.

Study description

Background summary

There is increasing interest in cognitive deficits after chemotherapy. In several neuropsychological studies in breast cancer patients treated with chemotherapy we and others found impairment in cognitive functioning. In a series of neurophysiological studies we also found abnormalities in brain functioning in this patient population. A recent study by our group showed, furthermore, converging evidence for neurocognitive problems from neuropsychological, neurophysiological as well as self-report measures up to five years after cessation of treatment with chemotherapeutics. In addition, our animal studies demonstrate 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. Despite these indications of long-lasting effects on the central nervous system resulting in persistent cognitive dysfunction, our understanding of the nature of cognitive impairment and the mechanism(s) driving this compromise is fragmentary at best.

Study objective

In our own recent studies we found indications of the existence of particular executive functioning deficits as well as memory impairments following different regimens of cytotoxic agents. Together with the indication from our animal study of a potential contributory role of reduced neurogenesis in the pathogenesis of the observed cognitive impairment and the availability of new and advanced MR techniques, compelling arguments are provided to initiate a study aiming:

1.To delineate a more specific neurotoxicity profile by studying brain activity with functional MRI during performance on tasks that are specifically sensitive to executive functioning and memory
2.To investigate anatomical changes in order to clarify underlying mechanism(s) by performing structural and chemical MR imaging
We will, in addition, examine whether there are indications that the pattern of abnormalities is modulated by type of cytotoxic regimen.
With the help of brain structural and functional morphology indices our understanding will be enhanced of the specific influence of cytotoxic agents on

brain functioning, its consequences and its underlying mechanism.

Study design

This one-year project is a joint venture of the department of Psychosocial Research and Epidemiology of the NKI-AVL and the departments of Radiology and Psychiatrics of the Academic Medical Center.

The study consists of two parts:

1) cross-sectional design
2) prospective design

Study burden and risks

Patients will be tested once (cross-sectional part) or twice (prospective part). Each test assessment will last two hours and consists of a semi-structured interview, several questionnaires, a practice session, and an MRI scanning session of one hour and 15 minutes. Half of the scanning time, the patient is actively engaged in task performance. The other half of the time, MR sequences are acquired for which no active involvement of the patient is required.

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. Ample experience with patient populations 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

all groups:
-female
-sufficient proficiency in the Dutch language;cross-sectional part:
-participation in previous neuropsychological study
-having been treated with high-dose chemotherapy (CTC);prospective part, experimental group
-newly diagnosed breast cancer patients without distant metastases that will receive chemotherapy (ACdd + T);prospective part, control group
-newly diagnosed breast cancer patients without distant metastases that will not receive chemotherapy

Exclusion criteria

-relapse and/or metastases
-excessive use of alcohol or drugs
-use of psychotropic medication
-neurologic or psychiatric disorders that may influence cognitive functioning
-conditions that preclude MRI examination

Study design

Design

Study type: Observational non 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):	01-07-2007
Enrollment:	40
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	NL17835.031.07