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

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In our recent studies we found indications of the existence of particular cognitive deficits as well as memory impairments following different regiments of cytostatic agents. Together with the indications form our animal studies of a potential...

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

Summary

ID

NL-OMON34510

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: KWF Kankerbestrijding

Intervention

Keyword: (f)MRI, chemotherapy, cognition

Outcome measures

Primary outcome

MRI 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-weigthed sequences followed by (automated) volumetric measurement, as a gross measure for tissue loss.

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

3. MR spectroscopy allows the safe in vivo measurement of brain neurochemistry. Compounds that can be identified are N-acetylaspartaat (NAA), choline (Cho) en myo-inositol (MI). NAA is contained almost exclusively within neurons and is considered a neuronal marker for neuronal density and viability. Cho indicates integrity of neuronal structure. 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 sequence 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 the dorsolateral prefrontal cortex.

Flanker task: previous studies by 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 (a central component of the neural circuit for action monitoring) is reliably observed during this task.

Paired associates task: a task concerning implicit memory. The medial temporal lobe (e.g. hippocampus) is reliably activated during encoding as well as retrieval of stimuli.

Resting state: subjects will be instructed to lie still, while no specific cognitive task is presented. These so-called resting state data contain information about several well-known brain networks, as well as the default mode network, which is thought to reflect baseline activity of the brain.

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. The neuropsychological tests will take place before the MRI scanning session.

The neuropsychological examination will consist of the following classical neuropsychological tests, which were also included in previous

neuropsychological examinations conducted at the NKI-AvL: Hopkins Verbal Learning Test, Stroop Color-Word Test, Trail Making Test, Verbal Fluency Test, Digit Symbol Test, Wechsler Memory Scale, PASAT, Fepsy Finger Tapping. 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), previous use of hormone replacement therapy, psychological distress (Hopkins Symptom Checklist), health related quality of life (EORTC QLQ-C30), self-reported cognitive problems (MOS questionnaire), self-reported medical history and medication use.

For the women 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. For the breast cancer patients not treated with chemotherapy, the following information will be obtained through the medical records: radiotherapy yes/no, endocrine therapy yes/no.

To study possible mediating effects of stress on the relation between chemotherapy and cognition, cortisol levels will be measured in hair samples.

Recent studies have indicated a possible mediating role for specific genetic polymorphisms, e.g. APOE, BDNF and COMT, in the development of cognitive dysfunction following chemotherapy. Therefore, saliva samples will be taken to screen for these genetic polymorphisms in relation to cognitive outcomes after cancer treatment.

Except for saliva sampling, all parameters will be measured during both

assessments.

Study description

Background summary

Over the last years, interest in cognitive deficits after chemotherapy has increased. In several neuropsychological studies in breast cancer patients we as well as others have found cognitive impairments after chemotherapy. In a series of neurophysiological studies we also found abnormalities in EEG measures in this patient population. A recent study by our group showed converging evidence for neurocognitive problems based on neuropsychological and neurophysiological measures and self-report of cognitive complaints up to five years after cessation of treatment with chemotherapeutic treatments. In addition, our animal studies have demonstrated long-lasting dose-dependent decreases in cell proliferation in the hippocampal formation in rats, after single intravenous administration of methotrexate. Despite these indications of long-lasting effects on the central nervous system, resulting in persistent cognitive impairment, our understanding of the nature and the mechanism(s) driving this compromise is fragmentary at best.

Study objective

In our recent studies we found indications of the existence of particular cognitive deficits as well as memory impairments following different regiments of cytostatic agents. Together with the indications form our animal studies of a potential contributory role of reduced neurogenesis in the hippocampus and the promising results of our pilot data, compelling arguments are provided to initiate a study aiming to:

1. Delineate a more specific neurotoxicity profile by studying brain activity with functional MRI during performance on tasks that are specifically sensitive to executive function and memory.

2. Investigate anatomical changes in order to clarify underlying mechanism(s) by performing structural and chemical MR imaging.

Study design

This prospective study with an observational design is a collaboration between the department of Psychosocial Research and Epidemiology and the department of neuro-oncology of the NKI-AvL and the department of Radiology of the Academic

Medical Center

Study burden and risks

All subjects will be tested twice, after surgery and before subsequent therapy and a year after completion of chemotherapy, or at yoked time intervals. Each test assessment will last two and a half hours and consists of a semi-structured interview, several questionnaires and neuropsychological tests, a practice session, and an MRI scanning session of one hour. During 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.
During both assessments, a small sample of hair will be collected to allow analysis of cortisol levels (see attached file with instructions about hair sampling). During interviews, patients indicated not to have any specific concerns regarding this measure. In addition, saliva samples will be taken during the first assessment to allow for genetic screening for factors related to cognitive functioning. Oral collection of saliva is a non-invasive and easy way to collect specimen for genetic analysis.
No information regarding individual performance, findings on individual cortisol measures or DNA analyses will be given in a standard way. All subjects will be given the opportunity to be informed about overall results of the study.

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, independent of menopausal status
-age under 70 years (to allow use of the same neuropsychological test battery)
-sufficient proficiency in the Dutch language;Experimental group:
-newly diagnosed breast cancer patients without distant metastases who will receive anthracycline-based chemotherapy ;Breast cancer control group:
-newly diagnosed breast cancer patients without distant metastases who do not require chemotherapy;Healthy control group:
-healthy females, matched for age

Exclusion criteria

All groups:
-previous malignancies
-excessive use of alcohol or drugs
-use of psychotropic medication
-neurologic or psychiatric disorders that may influence cognitive functioning
-conditions that preclude MRI examination.;Experimental group and breast cancer control group:
-relapse and/or metastases
- treatment with trastuzumab (Herceptin)

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:	Recruitment stopped
Start date (anticipated):	05-01-2011
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO Date:	04-08-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-04-2012
Application type:	Amendment
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	NL32148.031.10