Liquid Biopsy in Neuro-oncology in the St Antonius Hospital

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Implementation of liquid biopsy by NGS in cell-free circulating tumor DNA in CSF and / or blood, in patients clinically suspected of leptomeningeal metastases and / or brain metastasesDemonstrate that the detection of additional tumor mutations in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON49736

Source
ToetsingOnline

Brief title
LIBINOS

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Nervous system neoplasms malignant and unspecified NEC

Synonym
malignant meningitis, neoplasttic meningitis

Research involving
Human

Sponsors and support

Primary sponsor: Neurologie
Source(s) of monetary or material Support: Innovatie-fonds

Intervention

Keyword: Brain metastases, Cell-free DNA, Leptomeningeal metastases, Liquid Biopsy

Outcome measures

Primary outcome

The percentage of CSF / blood samples in which successful mutation analysis can be performed by liquid biopsy

The number and nature of additional mutations in CSF-ct DNA relative to blood and (if available) solid material of primary tumor
Relevant mutations concern mutations involved in therapy resistance and / or new targetable therapies, as described in (dynamic) online databases such as www.pharmgk.org or www.cpct.nl

Secondary outcome

- comparison between liquid biopsy findings in CSF versus routine parameters in CSF and / or radiological parameters, currently used for the diagnosis of leptomeningeal metastases
- correlation between CSF-ct DNA amount and specific mutations with clinical course and survival data
- course of tumor mutations over time, when there is a clinical indication for repeated lumbar punctures, and relationship of these mutations to the patient's neurological condition and therapy

future research goals

- detection of specific adhesion molecules or chemokines that play a role in

the trophism of solid CNS tumors

- detection of new targetable mutations by dd-PCR.

Study description

Background summary

Dissemination of cancer to the central nervous system (CNS) is a feared complication of a cancer. These metastases are localized in the brain parenchyma or leptomeninges including the cerebrospinal fluid - so called leptomeningeal metastases.
Brain metastases (BM) and leptomeningeal metastases (LM) may also co-occur. The highest propensity for CNS metastases are with small cell and non-small cell lung carcinoma, breast carcinoma and melanoma. Brain metastases incidence rates are reported between 9%-26%, and leptomeningeal incidence rates between 0,8- 8.%
Progression of disease in the CNS might occur despite good response of systemic disease to systemic cancer treatment - so called 'neuro-systemic dissociation'.
An example of this is CNS progression in female patients with HER-2 positive breast carcinoma treated with anti- HER directed therapies.
Lack of response of CNS metastases is often explained by insufficient drug penetration in the CNS compartment due to the Blood-Brain Barrier.
However CNS progression also occurs despite penetration of drugs in the CNS compartment. A likely explanation for this 'immunity' of CNS metastases is discordance of the metastases at a molecular level, as compared to the primary tumour. In solid material of brain metastases clinically informative new DNA mutations were detectable in approximately 50% of patients, not detectable in the primary tumour. These additional DNA mutations could either offer a molecular explanation for treatment resistance or offer new targetable mutations for the CNS metastases.
Translating this insight into clinical practice is hampered by the fact that solid material of brain metastases is not available in most patients with CNS metastases.
In the underlying study we will further explore the additional diagnostic and predictive value of so-called Liquid biopsy for patients who present with suspected CNS metastases in the Sint Antonius Hospital. The principle of liquid biopsy is that tumours shed parts in bodily fluids - for example as circulating tumour DNA (ct-DNA)- that can be isolated and analysed. The main advantage of liquid biopsy is that it is largely non-invasive- in contrast to traditional biopsy. Furthermore, it can better track tumours and mutations over a duration of time, and it may also be used to validate the efficiency of cancer treatment. There is increasing interest in tumour mutation detection (e.g. EGFR, BRAF, ALK) and treatment-resistance related mutations (e.g. T790M when using EGFR inhibitors, PIK3CA mutations when using anti-HER directed therapies)

in liquid biopsies. Detection of ctDNA in blood in metastasized cancer has been extensively studied and is increasingly used in clinical practice for example in breast cancer and non-small cell lung cancer.
The use of ctDNA detection in CSF is currently being explored in patients with leptomeningeal metastases and/ or brain metastases. Recent data suggest that ctDNA can also be isolated from CSF from patients which appear on MRI as *isolated* brain metastases without leptomeningeal involvement. Detection of tumour specific mutations in CSF may lead to a better understanding of therapy resistance of CNS metastases and improved future targeted treatment for CNS disease. Small series of LM and BM confirm that both digital droplet (dd-) PCR and Next Generation Sequencing (NGS) are applicable in CSF and can thereby identify respectively single or multiple cancer-driver- and resistance mutations.
In previous years liquid biopsy techniques have been developed at the Department of Clinical Chemistry in the SAZ with financial support of the Sint Antonius Innovation fund.

Study objective

Implementation of liquid biopsy by NGS in cell-free circulating tumor DNA in CSF and / or blood, in patients clinically suspected of leptomeningeal metastases and / or brain metastases

Demonstrate that the detection of additional tumor mutations in CSF-ct DNA, compared to the blood or (if available) primary tumor, has additional value in explaining therapy resistance and demonstrating targeted mutations in patients with CNS metastases of solid tumors

Study design

laboratory experimental, prospective cohort

A venipuncture is performed after the planned lumbar puncture. The tubes with extra cerebrospinal fluid and blood are handed over to the trial coordinator of the Laboratory for Clinical Chemistry.
Next generation sequencing (NGS) is performed with the Oncomine Pancancer cell-free assay in both CSF and blood, if available NGS is also performed on solid material of the primary tumor Particularly for the secondary research objectives, a limited number of patient and clinical parameters are obtained. These mainly concern the primary tumor, cancer treatment and course of disease. The liquid biopsy findings are compared with routine parameters with which the diagnosis of leptomeningeal metastases has been made, namely routine CSF parameters and results of neuro-imaging. The patient and clinical data are stored encrypted in Redcap
Presentation of the data is mainly descriptive - namely, the percentage of samples in which NGS analysis is successful, and the number of additional

clinically relevant mutations in CSF, relative to blood and solid material
Statistic analysis such as multivariate survival analysis will take place for the secondary outcome measures
All material (CSF and blood) and data will be retained until September 1, 2030 (5 years after completion of the study on September 1, 2025) and then destroyed. During this storage period, related residual material can still be examined - for example for specific new mutations or proteins - if new developments occur in this research area
In principle, all tests will take place in the SAZ. However, for possible confirmation of NGS test results, encoded material (CSF and blood), without patient data, can be sent to the NKI / AVL.

Study burden and risks

The burden of sampling includes the lumbar puncture and veni-puncture. There is no extra burden due to participation in this study except for the veni-puncture- as the lumbar puncture was already clinically indicated. The amount of CSF drawn is approx. 20 ml, of which 10 ml is used for ct DNA analysis, the amount of blood drawn approx. 60 ml. The risk of participation in this trial is therefore negligible. Patients also have no personal benefit as the investigation of new laboratory techniques does not influence current standard clinical care.

Contacts

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Selecteer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients who have a clinical indication for a diagnostic lumbar puncture because of secondary malignancy of the CNS (leptomeningeal metastases and/ or brain metastases) :
1/ age >18 years
2/ able and willing to give written consent
3/ able and willing to undergo lumbar puncture and venipuncture

Exclusion criteria

1/ if contra-indications for lumbar puncture are present
-skin infection
-coagulopathy
-signs or symptoms of increased intracranial pressure
-midline shift or obliteration of basal cisterns on neuro-imaging
2/ if a patient is unable or unwilling to give written consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-11-2020
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO

Date:	10-09-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL73502.100.20