Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients clinically suspected for leptomeningeal metastases

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Observational invasive

Summary

ID

NL-OMON41394

Source
ToetsingOnline

Brief title
N12CLM (Identification of Circulating tumor cells in CSF)

Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Nervous system neoplasms malignant and unspecified NEC
- Skin neoplasms malignant and unspecified

Synonym
leptomeningeal metastasis

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CSF, CTC, cytology

Outcome measures

Primary outcome

Determine the sensitivity and specificity of detection of circulating tumor cells (CTCs) in patients with Epcam expressing tumors compared to cytology in the cerebrospinal fluid of patients, clinically suspected for leptomeningeal metastases

Secondary outcome

- To determine the relationship between the number of CTCs in CSF and the patient*s neurological condition and Karnofsky performance score

- To determine the change in the CTC number between two sampling points and correlate this with the patient*s neurological condition and therapy

- To determine the relationships between demographics/tumor status and CTCs number in CSF.

- To determine the relationship between the CTC cells in the CSF and the CTCs in the peripheral blood

- To confirm EPCAM positivity in archived primary tumor tissue and tumorcells in CSF.

• To compare the predictive values of two CTC enumeration methods

- To investigate CNS distribution of tyrosine kinase inhibitors (e.g.

crizotinib,vemurafenib, dabrafenib, erlotinib, gefitinib, afatinib,

dacomitinib, trametinib and/or olaparib)

- To explore the levels of circulating tumor ctDNA in liquor

Study description

Background summary

Leptomeningeal metastases (LM), also known as meningeal carcinomatosis or neoplastic meningitis, is a diffuse dissemination of tumor cells into the cerebrospinal fluid (CSF) and leptomeninges.[1] Up to 8% of all patients with cancer develop LM. [2] The highest incidence of LM is seen in patients with (lobular) breast carcinoma (10%), small cell and non-small cell lung carcinoma (10%) and melanoma (5%).[3] Due to a spread of tumor cells in the CSF, LM is characterized by multifocal symptomatology (cerebral, cranial nerve and/or spinal nerve dysfunction). Gadolinium enhanced MRI of the symptomatic location of the nervous system is the radiological method of choice when LM is clinically suspected. In patients with a metastasized tumor, clinical signs of LM and contrast enhancement of either the leptomeninges, pia mater/cortex or cranial or spinal nerves on MRI, the diagnosis LM can be made. The sensitivity of MRI with gadolineum for LM is 75% and the specificity 77%. [4] If MRI does not show equivocal abnormalities, CSF cytology needs to be performed. In 55% of patients with LM from solid tumors, malignant cells are found during the first CSF examination. The sensitivity raises to 80-90% after the second CSF sampling, as determined in the pre-MRI era.[5] The volume of sampled CSF determines partly the sensitivity of CSF cytology. If possible, 10 ml CSF needs to be taken and the material must be processed as quickly as possible. Clinical chemical analysis of the CSF (leukocytes, lactate dehydrogenase, total protein, glucose) is aberrant in 90% of patients with LM.[5] An abnormal clinical chemical analysis of the CSF does not prove LM, but can also occur in other neurological diseases, including (infectious) meningitis.

Recently, Patel et al (2011) described the detection of breast cancer cells in the CSF using the Cell Search System (Veridex). [6] Using this method, the CSF is enriched immuno-magnetically for the epithelial cell adhesion molecule (EpCAM). Next nuclear staining with 4 ',6-diamidino-2-phenylindole (DAPI) and immunofluorescent detection with cytokeratin and CD45 is performed in 5 patients with leptomeningeal metastases from breast cancer and approximately 104 circulating tumor cells (CTCs) in 7,5 ml CSF were found, using this method. There seemed to be an association between the number of CTCs and

response to intrathecal administered chemotherapy in this small group of patients.

ALK, BRAF. EGFR, MEK and PARP inhibitors are oral targeted therapies in the treatment of breast cancer, lung cancer and melanoma. Since LM is common in these forms of cancer, gaining knowledge about the CNS distribution of these drugs is important. Clinical trials of vemurafenib, dabrafenib, trametinib and olaparib show encouraging results with respect to systemic metastases. However, they did not yet fully evaluate the distribution of these agents to the CSF.
By quantification of tyrosine kinase inhibitors (e.g. crizotinib,vemurafenib, dabrafenib, erlotinib, gefitinib, afatinib, dacomitinib, trametinib and olaparib) in CSF and in plasma the penetration of these agents through the blood-CSF barrier can be investigated.

Study objective

In the future, the determination of CTCs and ctDNA in the CSF could be a new quantitative method for the anti-tumor response assessment of systemic or intrathecal therapy (as opposed to CSF cytology, which is subjective and not a quantitative method). If the method shows greater sensitivity than CSF cytology and can reliably measure single tumor cells, the sensitivity of CSF examination in patients with a clinical suspicion of LM will increase. Possibly, this method can also be used to detect micrometastases in the CSF in patients without neurological symptoms, but with a high risk of CNS metastases

Study design

We will investigate a maximum of 100 patients, being treated at the NKI-AVL and Slotervaart Hospital for an Epcam positive tumor (breast cancer, lung cancer, gastrointestinal cancer, melanoma) and undergo a diagnostic lumbar puncture because of a clinical suspicion of LM.
Written informed consent will be obtained from patients prior to study start. From every patient a sample of 1 x 2 ml of CSF for chemistry (the rest material will be used for determining ctDNA), 1 x 5 ml of CSF for cytology and EPCAM/MCSP staining (in case cytology shows positive result) and 1 x of 5 ml of CSF for CTC enumeration will be taken by the neurologist or neurology resident (in total 12 ml CSF per sampling). From patients that are treated with tyrosine kinase inhibitors (e.g. crizotinib,vemurafenib, dabrafenib, erlotinib, gefitinib, afatinib, dacomitinib, trametinib and/or olaparib) 2 ml extra CSF for drug quantification will be taken (in total 14 ml CSF per sampling). One standard 8ml tube for chemistry and three extra 8 ml samples of whole blood for CTC assay will be drawn by blood sampling technitians (bloedafname)/OIO has also an NKI- AVL Statement of competence for venipuncture (bekwaamheidsverklaring voor venapunctie) - in total 32 ml blood per sampling), to determine the amount of CTCs in blood. one standard tube of blood for chemistry will be drawn. From patients that are treated with tyrosine kinase

inhibitors (e.g. crizotinib,vemurafenib, dabrafenib, erlotinib, gefitinib, afatinib, dacomitinib, trametinib and/or olaparib) 4 ml extra blood for drug quantification will be taken (in total 36 ml blood per sampling). If more lumbar punctures would be clinically indicated, extra sampling as stated above will be performed. If available, archived primary tumor tissue will be obtained for EPCAM staining.

Study burden and risks

The CTC sampling of the CSF will be done by during a planned diagnostic lumbar puncture for cytology and chemical analysis of the CSF. CTC blood sampling will be done during standard blood sampling, directly before or after the lumbar puncture. 1 extra tube of CSF and 3 extra tubes of blood samples will be drawn for purpuses of this study. From patients treated with tyrosin kinase inhibitors (e.g. vemurafenib, dabrafenib, trametinib, crizotinib, erlotinib, gefitinib, afatinib, dacomitinib, and olaparib) 2 another 2 ml CSF and 4 ml blood will be taken.

When the patient visits the NKI-AVL for blood and CSF sampling, the following medical information will be collected: gender and date of birth, detailed diagnosis based on existing pathology reports, current stage and status of disease, treatment history and current treatment, co-medication, neurological signs and symptoms and Karnofsky performance score. After sampling and data registration, on day 3 the nurse practitioners will call patients to collect information about possible adverse events from collecting extra material. If no related adverse events occur the participation is finished.

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. Patients who are treated for advanced EpCam positive solid tumors (such as breast cancer, lung cancer, gastrointestinal cancer) or melanoma
2. Age >=18 years;
3. Able and willing to give written informed consent;
4. WHO performance status of 0, 1, 2, 3 or 4;
5. Able and willing to undergo lumbar puncture and veni-puncture.

Exclusion criteria

Lumbar puncture not clinically / diagnostically indicated

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):	22-10-2012
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	30-05-2012
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-08-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-10-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2015
Application type:	Amendment
Review commission:	METC NedMec

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	NL40016.031.12