Circulating tumor cells and driver mutation analysis in cerebrospinal fluid in patients with epithelial tumors with suspected leptomeningeal metastasis

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Introduction: Two to five percent of patients with solid tumors develop leptomeningeal metastases (LM). Diagnosis of LM can be based on clinical symptoms and typical contrast enhancement of the leptomeninges on MRI brain and/or spine. However, MRI has a low sensitivity (76%) and specificity (77%) for the diagnosis of LM. When MRI is normal or results are inconclusive, a lumbar puncture (LP) is performed to obtain cerebrospinal fluid (CSF). Sensitivity of CSF cytology is also low: 44-67% at first LP, increasing to 84-91% upon second sampling. To improve CSF diagnostics, enumeration of Circulating Tumor Cells (CTC) by immunoflow cytometry has been developed. To determine selected driver mutations Droplet Digital PCR (ddPCR) can be used.

Aim: To determine the sensitivity and specificity of a diagnostic immunoflow cytometry method in CSF in patients with epithelial tumors with suspected LM. To explore the distribution of driver mutations in cell free CSF and isolated CTCs from CSF.

Methods: We developed an epithelial cell adhesion molecule (EpCAM)- based immunoflow cytometry assay to detect CTC in the CSF. We tested the performance of this assay versus CSF cytology in CSF in a prospective study in patients with solid tumors with a clinical suspicion of LM but a non-confirmatory MRI. In a subset of the cohort we analyzed the primary tumor, plasma, cell free CSF and CTC isolated from CSF for selected driver mutations by ddPCR.

Results: In the first 55 patients with solid tumors with a clinical suspicion of LM but a non-confirmatory MRI, CSF cytology had a sensitivity of 68% (48-83) (95% CI) and a specificity of 100% (84-100). At a cut-off value of >1 CTC/ml the CTC assay had a sensitivity of 93% (76-99) and a specificity of 100% (83-100). We detected driver mutations in the primary tumor, plasma, cell free CSF and isolated CTCs from CSF. CTCs isolated from CSF were positive for the driver mutation in patients with LM from a tumor with known driver mutation, while simultaneously analyzed leukocytes were wild-type positive and negative for the driver mutation. At Figon 2018 updated results will be presented.

Conclusion: The EpCAM- based immunoflow cytometry assay can identify CTC in CSF in patients with LM with a negative cytology. ddPCR can be used to determine the driver mutation in cell-free CSF and isolated CTCs from CSF.