Circulating Tumor Cells in Breast Cancer patients with Leptomeningeal Metastases: Detection and in vitro Expansion

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Background & objectives

The incidence of breast cancer (BC)-related leptomeningeal metastases (LM) seems to be increasing, due to the improvement of survival of patients with metastatic BC and the poor diffusion of therapeutic agents into the central nervous system (CNS). The diagnosis of BC-related LM relies on the detection of tumor cells in cerebrospinal fluid (CSF) using conventional cytology. However, the sensitivity of this technique is low. Circulating tumor cells (CTCs) have become a reliable biomarker in the liquid biopsy field for metastatic cancer for 20 years.

Methods

In a prospective monocentric study, we evaluated the clinical sensitivity and specificity of CTC detection in CSF for LM diagnosis compare to conventional CSF cytology.

Results

Standard cytology was positive in 18/40 patients and CTCs were also detected in these 18 patients (median: 5824 CTC, range: 93 to 45052). The detection of ≥1 CSF CTC was associated with a clinical sensitivity of 100% (95% CI, 82.4–100) and a specificity of 77.3% (95% CI, 64.3–90.3) for LM diagnosis. In the context where the CellSearch® system is associated with fewer organizational constraints: analyzed within 96 h after lumbar puncture *vs* 1 h for cytology and requirement of a unique sample *vs* 3 for cytology, this option should be investigated in a larger cohort. Additionally, $HER2^+$ CTCs were detected in the CSF of 40.6% of patients with $HER2^-$ BC, suggesting that the HER2 status of LM should be evaluated to increase the treatment opportunities for these patients.

Conclusion

Furthermore, the high number of CTCs found in the CSF of these LM-BC patients leads us to investigate CTC cultures from this enriched and pure biological fluid. Indeed, the cells that are able to survive and grow *ex vivo* are rightly said to be the most aggressive metastasis-initiator cells and, thus, represent the best model to study the biology of LM metastases and generate new knowledge likely to have an impact on cancer management. Recently, we succeeded in establishing new breast CTC lines (n=2 from one patient) from the peripheral blood of a triple negative breast cancer patient with LM. This new model will allow us to access new knowledge for this specific subtype of BC, which clearly lacks appropriate therapies.