https://doi.org/10.29289/259453942021V31S2008

CIRCULATING TUMOR DNA OF CEREBROSPINAL FLUID SAMPLES IN TRIPLE-NEGATIVE BREAST CANCER: USEFULNESS OF LONGITUDINAL ASSESSMENT FOR EARLY DETECTION OF BRAIN METASTASIS

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Objectives: Triple-negative breast cancer (TNBC) still has poor prognosis for a higher rate of relapse and a greater tendency of developing brain metastasis (BrM) compared with other major breast cancer subtypes. Circulating tumor DNA (ctDNA) represents a valuable tool associated with the outcome and the aggressiveness of breast cancer. Biomarkers allowing to predict the development of BrM in TNBC are needed. We studied the usefulness of assessment of CSF-ctDNA for identification early at-risk patients to develop BrM in TNBC. **Methodology:** A total of 323 newly diagnosed nonmetastatic TNBC patients who underwent neoadjuvant therapy + surgery (NACT) with complete response (CR) were prospectively enrolled. After surgery, CSF-ctDNA collected from all patients enrolled was extracted and assessed using the QIAamp Circulating Nucleic Acid Kit. Survival curves were estimated by using Kaplan–Meier method and compared with the log-rank test. Multivariate Cox regression was used to identify the risk of mortality at 3 years. **Results:** After NACT, CSF-ctDNA was detectable in 126/323 (39%) patients, 101/126 (80%) were diagnosed at Stage 3. A total of 124 out of 126 (98.4%) ctDNA+ patients subsequently developed BrM. In contrast, only 2 (2/197, 1%) ctDNA– patients subsequently developed BrM and 195 other patients remain in a CR ($p<0.001$, Fisher's exact test). CSF-ctDNA did associate with PFS and OS: undetectable ctDNA was associated with superior PFS (HR 0.3; $p=0.002$) and OS (HR 0.2; $p<0.01$), indicating survival is largely determined by the onset of BrM. With a median follow-up of 3 years, median PFS of ctDNA+ versus ctDNA– patients was 13 months versus not reach, $p=0.004$ (log-rank test). Median OS for ctDNA+ versus ctDNA– patients was 16 months after NACT versus not reach, $p=0.0016$ (log-rank test). At multivariate analysis, detectable CSF-ctDNA emerged as the best predictor of the development of BrM and 24-month mortality (HR: 3.62; $p<0.0001$). Age, stage, Ki67%, and response to chemotherapy were not significantly associated with the prognosis. **Conclusion:** After NACT, detectable CSF-ctDNA significantly associated with PFS and OS, identifying early at-risk patients to develop BrM in TNBC who should take advantage from appropriate additional treatment, remains a critical problem.

Keywords: Triple-Negative Breast Cancer; Brain Metastasis; Circulating Tumor DNA; Liquid Biopsy; Predictive Biomarkers.