p53-binding protein 1 accumulation in circulating tumor cells identifies chemotherapy-responsive metastatic breast cancer patients

Fabienne Schochter[1]
Kathrin Niedermayer[1], Cäcilia Köstler[2], Barbara Alberter[2], Volkmar Müller[3], Hans Neubauer[4], Tanja Fehm[4], Thomas W. P. Friedl[1], Bernhard Polzer[2], Wolfgang Janni[1], Brigitte Rack[1] and Lisa Wiesmüller[1]
[1] Department of Obstetrics and Gynecology, Ulm University
[2] Division of Personalized Tumor Therapy, Frauenhofer-Institute for Toxicology and Experimental Medicine
[3] Department of Gynecology, University Medical Center Hamburg-Eppendorf
[4] Department of Obstetrics and Gynecology, University of Duesseldorf

Background & objectives

Triple-negative breast cancer (TNBC), diagnosed in 10-15% of all metastatic breast cancer (MBC) patients, includes very heterogenous tumors. A high prevalence of gene mutations and epigenetic changes result in BRCAness, compromising safe DNA repair through homologous recombination repair (HRR). The DNA end-binding protein p53-binding protein 1 (53BP1) is crucial in protecting DNA ends in BRCA1-defective cells from resection and entry into error-prone repair pathways. Evidence suggests that it is down-regulated in subsets of breast cancer which is associated with poor prognosis. Circulating tumor cells (CTCs) provide accessible "biopsy material" to track cell traits and functions and their alterations during treatment and have already been proven to have a prognostic relevance in the adjuvant setting and MBC.

In this study we prospectively monitored the 53BP1 status in CTCs from 67 MBC patients with HER2- CTCs and known hormone receptor (HR) status of the primary tumor and/or metastases before, during, and at the end of chemotherapeutic treatment with Eribulin in order to determine its predictive value for therapeutic response.

Methods

CTCs from patient samples were identified using the Cellsearch® technology by subjecting them to EpCAM-based ferrofluid selection, immunostaining and image analysis. HER2 and 53BP1 status was determined by image analysis using DEPArray™ technology.

53BP1 expression of seven TNBC and four non-TNBC cell lines was determined using Western Blot analysis. Nuclear 53BP1 and γH2AX staining and genomic integrity were evaluated by immunocytochemical and whole-genome-amplification-based polymerase chain reaction (PCR) analysis, respectively.

Results

Comparative analysis of CTCs from patients with triple-negative and HR+ tumors revealed elevated 53BP1 levels in CTCs from patients with HR+ metastases, particularly following chemotherapeutic treatment. Differences in nuclear 53BP1 signals did not correlate with genomic integrity in CTCs at baseline or with nuclear γH2AX signals in MBC cell lines, indicating that 53BP1 detected features beyond DNA damage. Kaplan-Meier

analysis revealed an increasing association between nuclear 53BP1-positivity and progression-free survival (PFS) during chemotherapy until the final visit.

Conclusion

Summed up, our data suggest that 53BP1 detection in CTCs could be a useful marker to capture dynamic changes of chemotherapeutic responsiveness in triple-negative and HR+ MBC.