ctDNA BRCA1-methylation can predict therapy efficacy in ovarian and breast cancer patients.

Simon Joosse[1]
Annabelle Lobermeyer[1], Mina Netkova-Heintzen[1], Nikhil Kalra[1], Maximilian Wankner[1], Paul Rademacher[1], Sandra Lenz[1], Alexander Sartori[2], Darryl Irwin[2], Leticia Oliveira-Ferrer[1], Linn Woelber[1], Volkmar Mueller[1], Barbara Schmalfeldt[1], Katharina Prieske[1] and Klaus Pantel[1]
[1] University Medical Center Hamburg-Eppendorf
[2] Agena Bioscience

Background & objectives

Homologous recombination (HR) deficiency in ovarian and breast cancer is associated with increased sensitivity to platinum and PARP-inhibitor therapies. It is currently unclear whether the response to these therapies is also linked to HR-deficiency triggered by promoter hypermethylation of tumor-suppressor genes such as *BRCA1*. As methylation status can change during cancer progression, monitoring promoter methylation using cell-free DNA (cfDNA) as a "liquid biopsy" may help predict therapy efficacy. Therefore, we aimed to correlate *BRCA1*-methylation in tumor tissue and blood of ovarian and breast cancer patients to survival and treatment efficacy.

Methods

A meta-analysis was performed on all available studies containing *BRCA1*-methylation data and ovarian cancer patient survival. Primary and recurrent tumor tissue was obtained from surgery, whereas blood was obtained prior, during, and after chemotherapy. From the tissue and blood, (cf)DNA was extracted and *BRCA1*-methylation status was determined by methylation specific PCR and Agena's MassARRAY System.

Results

Although we could show that hypermethylation of the *BRCA1* gene promoter/enhancer region leads to mRNA downregulation, our meta-analysis including 2636 ovarian cancer patients across 15 studies showed no survival benefit of *BRCA1*-methylation, nor could platinum sensitivity be predicted. However, in a comparison between primary and recurrent ovarian cancer tumors, we confirmed that *BRCA1* promoter hypermethylation is unstable and is lost in recurrent disease. Over 250 blood samples were collected from 100 high-grade serous ovarian and triple-negative breast cancer patients. Approximately two-thirds of the ovarian cancer patients exhibited *BRCA1*-methylation at baseline of which a fourth lost hypermethylation during a median follow-up of 40 months. Multivariate survival analyses indicate that

hypermethylation and methylation conversion are independently correlated to longer relapse-free survival. Similarly, methylation patterns in cfDNA of triple-negative breast cancer patients correlated to disease status.

Conclusion

Methylation and methylation conversion correlated with disease outcome and patient survival. We expect that our results will be beneficial for ovarian and breast cancer patients who are initially sensitive to platinum-based chemotherapy or PARP-inhibitors due to *BRCA1*-methylation associated homologous recombination deficiency, but develop therapy resistance after methylation conversion. Monitoring the methylation status by liquid biopsy may be further developed as marker for predicting therapeutic response in ovarian and breast cancer patients.