PO-495 PREDICTION OF CHEMOTHERAPY SENSITIVITY ON ASCITES OF OVARIAN CANCER PATIENTS

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Introduction In epithelial ovarian cancer (EOC) patients, 15%–20% of the tumours do not respond to first-line chemotherapy treatment, i.e., paclitaxel combined with a platinum-based therapy. The aim of this pilot study was to validate a new approach to measure the sensitivity of ovarian cancer cells to chemotherapeutics. Furthermore, we aimed to relate the in vitro response of tumour cells from ascites to clinical response of ovarian cancer patients.

Material and methods For this pilot study, we selected 18 patients with advanced stage EOC and collected ascites. Proliferation assays on tumour cells isolated from the ascites were performed using intracellular ATP content as an indirect measure of cell number. Clinical outcome was determined using status of remission after primary treatment, disease free survival (DFS), and the platinum-sensitivity. Complete remission was defined as a serum-CA125 <35 E/ml, a complete or optimal debulking surgery, and a complete response on CT-scan. We related the sensitivity tests and the clinical outcome using descriptive statistics.

Results and discussions The outcome of the proliferation assays, expressed by Gl50 and using dose-response curves, corresponded to the clinical outcome in the patient in most cases. Of the 14 ascites samples eventually tested, seven of the in vitro responses were poor as well as the DFS of the patient. Four samples showed good in vitro response and the patient showed a good DFS as well. Only two of the samples tested did not show similarity in in vitro response and in clinical outcome of the patient. We also determined the in vitro response to second line therapies and new targeted therapies, including PARP- and bromodomain inhibitors.

Conclusion This pilot study demonstrates the feasibility of using ascites tumour cells to perform drug sensitivity tests. These are promising results because it seems possible to predict accurately the response on first-line chemotherapy in advanced stages of EOC. However, larger observational studies are required to show a statistical significant relation, to determine the best clinical response measurements and to test second line therapies.

PO-496 INTEGRATED OMICS-BASED APPROACH TO THE IDENTIFICATION OF SPECIFIC EXPRESSION PROFILES ASSOCIATED WITH PTEN-LOSS

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Introduction PTEN is a protein that restrains cells from growing unchecked; when it is absent or not functioning (as it often happens in prostate and colorectal cancer - CRC), cancer develops more easily and grows in a more aggressive and therapy-resistant fashion. However, just measuring PTEN mutational status or gene/protein levels in clinical samples may not be sufficient to assess its function, as its regulation is complex. Therefore, we analysed miRNA, transcriptomic, and proteomic profiles of isogenic CRC models differing for PTEN status, in order to identify a set of genes or proteins that are stably modulated by the presence or absence of a functional PTEN.

Material and methods To identify biomarkers of PTEN loss of function and functional downstream effectors of PTEN activity, the isogenic CRC cell lines HCT116 (PTEN+/+) and HCT116 PTEN−/− (Horizon Discovery Ltd) were subjected to comprehensive miRNA profiling (Human miRNA Microarray Release 21, Agilent), transcriptomic analysis (NextSeq 500, Illumina), and semi-quantitative phosphoproteomic analysis (Antibody Microarray Service, KinexTM).

Results and discussions miRNA profiling found 18 miRNAs differentially expressed in HCT116 PTEN−/− and their HCT116 PTEN+/+ counterpart: only miR-196a-5p is up-regulated in HCT116 PTEN−/−, whereas other 17 miRNAs were all down-regulated; several of these target miRNAs have been validated by qRT-PCR. RNA-Seq data were analysed via the RAP pipeline available at CINECA that relies on the Tuxedo suite (Tophat-Cufflinks-Cuffdiff) for read mapping, transcript abundance estimation and transcript or gene-based differential expression. RNA-Seq analysis showed 247 differentially expressed genes in HCT116 PTEN−/− cells as compared to HCT116 PTEN+/+ (159 up-regulated and 88 down-regulated in HCT116 PTEN−/−) and clustering into 9 subgroups (including: tissue morphogenesis; negative regulation of phosphatase metabolic process; regulation of sequence-specific DNA binding transcription factor activity). qRT-PCR assay of 10 dysregulated genes was performed to validate the RNA-Seq data set. Proteomic analysis showed that 92 proteins (25 total proteins and 67 phospho-proteins) are differentially expressed in HCT116 PTEN−/− and their HCT116 PTEN+/+ counterpart, some of which have been validated by WB.

Conclusion Our data identify differentially expressed sets of miRNAgenes/proteins between HCT116 PTEN−/− and HCT116 PTEN+/+. Bioinformatics analysis to cluster these sets into functional PTEN-loss ‘signatures’ is ongoing.
COMPARISON OF EXPRESSION OF MIR21

A NOVEL ROLE FOR JUNCTIONAL ADHESION RECEPTOR Molecule-A (JAM-A) IN HER2-POSITIVE GASTRO-OESOPHAGEAL CANCERS

Introduction miR-21 is an oncomir that is overexpressed in many types of solid tumours. According to some studies miR-21 expression is higher in breast tumours than normal breast tissue and it is significantly correlated with shorter survival of patients. Many studies have focused on miR-21-5p and its correlation with clinic pathological features and survival of breast tumours. In some of the studies miR-21-5p expression has been shown to be associated with ER status, PR status, HER2 status, clinical stage, lymph node, tumour grade and size. The purpose of this study was to compare the expression of miR-21-3p and miR-21-5p in progression of breast tumours and their association with corresponding clinic pathological data from the breast cancer patients.

Material and methods Six non-neoplastic breast tissues and 144 tumours, from breast cancer patients diagnosed 1987–2003, were obtained from the Department of Pathology at Landspitali University Hospital. The expression levels of miR-21-3p and miR-21-5p were measured with StepOnePlus Real-Time PCR System by applying EXIQON primer sets and SYBR Green master mix using miR-16-5p as endogenous control.

Results and discussions miR-21-5p was expressed at significantly higher levels than miR-21-3p in both normal (p=0.0003) and tumour tissues (p=6.378e-12). A significant difference was not observed between miR-21-5p expression in normal breast tissue and tumours. High miR-21-5p expression correlated significantly with HER2 expression (p=0.001) but it did not correlate with other clinical and pathological factors or survival. miR-21-3p was expressed at significantly higher levels in tumour tissues than normal breast tissue (p=0.003). Its expression was significantly higher in tumours from patients with metastasis than without metastasis (p=0.02). Furthermore, higher levels of miR-21-3p correlated with shorter disease free survival (p=0.03, HR=1.72, 95% CI=1.03–2.9).

Conclusion Although miR-21 is one of the most studied and upregulated miRNAs in human solid tumours the comparison of miR-21-3p expression with miR-21-5p expression in breast tumours has not been well studied. Our results suggest that miR-21-3p could be a better indicator of breast cancer progression than miR-21-5p. More studies in larger breast cohorts and functional cell based assays will be needed to shed light on the potential role of miR-21-3p in breast tumours progression.

REFERENCES

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