1134 POSTER

Epithelial-to-Mesenchymal Transition and Ovarian Carcinoma: New Insights in Response Prediction to Standard Treatment

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Background: Ovarian carcinoma is the fourth most common cancer in women and the leading cause of gynaecological cancer-related mortality in the western countries. The management of ovarian cancer involves citorreductive surgery followed by a combination chemotherapy regimen that includes paclitaxel and a platinum compound (carboplatin or cisplatin). Outcome is significantly improved with this regimen, thus 40 to 50% of patients achieve a complete clinical remission. There is a crucial need to identify new biomarkers predictive of response to the standard treatment. Recently, tumour microenvironment has become an attractive target in gynaecological malignancies. In ovarian carcinoma, acquisition of invasiveness is accompanied by the loss of the epithelial features and the gain of a mesenchymal phenotype, a process known as epithelial-mesenchymal transition (EMT). In pre-clinical settings, EMT is related to tumour progression and resistance to chemotherapy. We focus on a selected group of genes related to this process, to identify a gene expression profile as a predictive marker for response to treatment.
Materials and Methods: Patients (n = 84) were staged according to the International Federation for Gynecology and Obstetrics (FIGO) classification. Optimal debulking was defined as $\leqslant$1 cm (diameter) residual disease. A complete response (CR) was defined as absence of all clinical/radiographic evidence of disease. Specific TaqMan Gene Expression assays for 43 genes were selected and gene expression was determined by qRT-PCR with TaqMan Low Density Arrays (Applied Biosystems). We applied a normalization factor based on the geometric mean of four housekeeping genes, selected by Genorm Software. A Logistic regression analysis was used to build multiple models based on the combination of significant genes, selected by the Akaike Information Criterion and the Harrell index. The accuracy of the model was determined by using the receiver operating characteristics (ROC). SAS 9.1, Enterprise Guide 3.0 and SPSS (version 9.0; SPSS Inc Chicago, IL, USA) packages were used for statistical tests. Leave-one-out cross validation to avoid over-estimation was performed using R language version 2.2 with the Design Software package version 2.0.
Results: We identify a 6 gene expression profile related to EMT. The area under curve (AUC) were 0.868 (0.791–0.946) and 0.809 (0.716-.902) after leave one out cross-validation, both with a p value <0.001. In a multivariate analysis, both the profile and the debulking status were independently associated with clinical response.
Conclusions: We found a 6 gene expression profile, related to EMT process with predictive value for response in advanced ovarian carcinoma. Even thought, an independent validation is necessary to confirm these data.

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Proteomic Anlaysis of Differenially Expressed Proteins in Patients With Metastatic Colorectal Cancer Responding to Bevacizumab

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Objective & Background: Treatment of patients with metastatic colorectal cancer includes chemotherapy and a monoclonal antibody (Cetuximab or Bevacizumab). Patients who have k-ras mutated tumours are given Bevacizumab. However, no biomarker exists to determine those patients who will respond to this targeted treatment. The objective of this study was to investigate the differential protein expression between patients who do and do not respond to bevacizumab and compare this with normal controls.
Methods: Serum from 24 patients diagnosed with metastatic colorectal cancer and 11 normal controls were collected pre-treatment and stored. All patients received Bevacizumab along with chemotherapy. Progression free and overall survival data was collected on all patients. Serum was depleted of high abundant proteins and protein expression analysed using fluorescence two-dimensional differential in-gel electrophoresis (2 D-DIGE). Gels were scanned using a Typhoon 9410 Variable Mode Imager (GE Healthcare). The images were cropped (ImageQuant 5.2, GE Healthcare) and exported into Progenesis SameSpots v3.3 (Nonlinear Dynamics, UK) for quantitative analysis.
Results: 80 spots were differentially expressed between responders and non-responders of Bevacizumab, and of these, 10 spots had significant power (80%) to be carried forward for subsequent mass spectrometry analysis. 214 spots were differentially expressed between cancer patients and normal controls ($p < 0.05$) and 99 of these had power >0.8.
Conclusion: There is a significant difference in protein expression patterns between responders and non responders to Bevacizumab. Mass spectrometry is currently identifying these proteins which could used as potential biomarkers of response to Bevacizumab and help us understand resistance to this targeted therapy.

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Association of Common Variants of GSTP1, GSTA1 and TGFβ1 Genes With the Risk of Radiation-induced Subcutaneous Fibrosis in Breast Cancer Patients

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Background: In order to provide new insights on the genetic basis of normal tissue radiosensitivity, we evaluated the association between eight polymorphic variants located in six genes related to DNA repair mechanisms, oxidative stress and fibroblast proliferation (XRCC1 Arg399Gln, XRCC1 Arg194Trp, TP53 Arg72Pro, GSTP1 Ile105Val, GSTA1 C-69T, eNOS G894T, TGFβ1 C-509T, TGFβ1 T869C) and the risk of subcutaneous fibrosis in a retrospective series of patients who received radiotherapy after breast conserving surgery.
Methods and Materials: Subcutaneous fibrosis were scored according to the LENT-SOMA scale in 257 breast cancer patients who underwent surgery plus adjuvant radiotherapy. Genotyping was conducted by PCR-RFLP analysis on genomic DNA extracted from peripheral blood. The association between genetic variants and the risk of moderate to severe fibrosis was evaluated by binary logistic regression analysis.
Results: Two hundred thirty-seven patients were available for the analysis. Among these, 41 patients (17.3%) developed moderate to severe fibrosis (G2−3) while 196 (82.7%) patients displayed no or minimal fibrotic reactions (G0−1). After adjustment of confounding factors, GSTP1 Ile105Val (OR: 2.660, 95% CI: 1.169–6.051, P = 0.019), GSTA1 C-69T (OR: 3.109, 95% CI: 1.150–8.405, P = 0.025) and TGFβ1 T869C (OR: 0.281, 95% CI: 0.085–0.926, P = 0.036) polymorphisms were found to be significantly associated with the risk of G2−3 radiation-induced fibrosis. In the combined analysis, carriers of 3 risk genotypes were found to be at higher odds to develop G2−3 fibrosis compared to patients with 2 risk genotypes (OR: 3.986, 95% CI: 1.420–11.188, P = 0.009) or 0−1 risk genotype (OR: 8.235, 95% CI: 2.598–26.096, P = 0.0003).
Conclusions: These results suggest that functional variations in genes involved in oxidative stress response and fibroblast proliferation may modulate the development of radiation-induced fibrosis in breast cancer patients. Results of the combined analysis support the notion that approaches based on the combination of different genetic markers have the potential to predict normal tissue responses.

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Is MMP-9 Q279R a Possible Marker of Prognostic in Non Small Cell Lung Cancer?

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Background: Lung cancer is the leading cause of death by cancer in the world, originating about 17.5% of total deaths from cancer (1.18 million). The extracellular microenvironment is a dynamic entity and provides regulatory signals on an intricate network of pathways that include cell adhesion, differentiation, division and apoptosis.
Matrix metalloproteinases (MMP), comprise a family of proteolytic enzymes which are involved in the regulation of various cell behaviours, including cancer cell growth, differentiation, apoptosis, migration, invasion, and the regulation of tumour angiogenesis and immune surveillance. MMP-9 overexpression contributes to cancer development and progression. A nonsynonymous A to G transition in exon 6 of *MMP9* leading to a substitution of arginine by glutamine at position 279 (*MMP9 Q279R*; rs 17576) has been shown to affect the substrate binding capacity. The aim of this study was to evaluate the influence of this polymorphism in the overall survival of non-small cell lung cancer (NSCLC) patients.
Material and Methods: Caucasian patients(n = 156) admitted to the Portuguese Institute of Oncology of Porto (IPO-Porto), Portugal, with cytological or histological confirmed NSCLC, have been prospectively