Conclusions: This is the first study reporting that A870G *CCND1* polymorphism could act as a cofactor of HPV in the initiation of cervical carcinogenesis, supporting evidence for a genetic factor on ICC risk. Our data suggest that A870G *CCND1* polymorphism is associated with the susceptibility to ICC and supports evidence for a site-specific prevalence of genetic alterations. These results may be important in the definition of a biological predictive profile for the development of ICC.

165 ORAL

GSTM1 genotypes as predictive biomarkers in ovarian cancer

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Background: Ovarian cancer is an aggressive disease with high mortality. It is well established that Platinum-based chemotherapy is limited by significant inter-individual variations in responses which can often be explained by genetic alterations in drug-metabolizing enzymes. The glutathione S-transferases (GSTs) are a group of multifunctional enzymes that catalyze the conjugation of glutathione with a variety of electrophilic compounds, including cytotoxic agents. A significant percentage of normal individuals exhibit genetic polymorphism with a homozygous deletion (null genotype) of the genes, leading to absence of the enzyme.
Methods: In the present study we analyzed *GSTM1* and *GSTT1* polymorphisms in the genomic DNA isolated from peripheral blood of 129 patients with ovarian cancer treated with chemotherapy (paclitaxel and cisplatinum) after cytoreductive surgery and assessed its correlation with the clinical outcome of these patients. The median follow-up for the patients was 41 months (4 to 105 months).
Results: The estimated 5-years survival rate was 68% for all patients and 52% for carriers of GSTM1-wt (wt indicates wild type) compared with 80% for GSTM1-null genotype carriers. The median survival time was significantly better in patients who are carriers of the GSTM1-null genotype (102 vs.61.63 months; $p = 0.0022$). The progression free interval was more favorable for GSTM1− null carriers (55 vs. 25 months; $p = 0.0042$). Comparing GSTT1-wt with GSTT1-null we didn't observe any statistically significant differences in the median survival time ($p = 0.6613$) and the progression free interval ($p = 0.9304$).
Conclusions: The study suggests that characterization of the drug-metabolizing genetic individual profile can be of great interest in clinical oncology. It can define the optimal chemotherapy for each patient, improve the efficacy and reduce the poor drug responses. The GSTM1-null genotype seems to be a good predictive biomarker in ovarian cancer.

166 ORAL

Genetic polymorphisms in glutathione-s-transferases as prognostic factors in surgically treated lung cancer patients

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By investigating the prognostic value of genetic polymorphisms in glutathione-*S*-transferases (GST), the present study tried to identify patients at risk of enhanced mortality after lung cancer surgery. Genetic polymorphisms can affect enzyme stability, substrate specificity and activity, thereby influencing the individual capability to eliminate xenobiotics and endogenous reactive products. This study investigated *GSTA1* (−69C>T), *GSTM1*, *GSTO1* (419C>A and 464−465delAG, IVS4+1delG), *GSTP1* (313A>G(and *GSTT1*.
The current study involved 384 patients (308 men and 76 women), a representative cross section of Caucasian lung cancer patients who were curatively treated by surgery, recruited from 1997 till 1999 at the Thoraxklinik Heidelberg and followed up for vital status through 2004. DNA was isolated from peripheral blood. Genotypes were determined by PCR and capillary PCR followed by fluorescence based melting curve analysis. Validity of SNP-results was confirmed by PCR-RFLP. In addition different therapy schemes, demographic factors, occupational exposure, smoking status, pack-years, performance status (PS) and tumor specific factors such as histology, grading, localization, pTNM, stage and R-status were recorded. Overall survival was assessed by Kaplan-Meier-survival function and Cox's proportional hazard regression model for multivariate analysis.
Median follow-up was 77.5 months (95%CI: 72.9−82.1), median survival was 38.9 months (95%CI: 29.6−48.2). Significant associations with survival were observed for stage, pN (0 vs > 0), pM (0 vs 1), R-status (0 vs > 0), age (< 70yrs vs > 70yrs) and PS (0 vs > 0). Further analyses included only patients where complete resection of the tumor was achieved (n = 343). Among the GST-genotypes investigated, univariate analyses identified a significantly ($p < 0.05$) better prognosis to be associated with *GSTP1 GG* vs *AG/AA* genotype, especially in smokers. In subgroup analyses the *GSTM1 non-null* genotype was associated not significantly with better prognosis of either ex-smokers or patients with stage IIIA tumors ($p = 0.07$ and $p = 0.06$, respectively).
In conclusion, our findings from one of the largest studies conducted so far on this topic, may contribute to improve the prognosis of lung cancer patients by allowing more efficient post-surgery treatment and aftercare. Results from studies of other groups which involved fewer patients and had less follow-up time could not be reproduced.
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167 ORAL

The XPD lys751gln polymorphism in colorectal cancer patients treated in first line chemotherapy with 5-FU–oxaliplatin or 5-FU–irinotecan combinations: a prognostic factor or a predictive marker of oxaliplatin efficiency?

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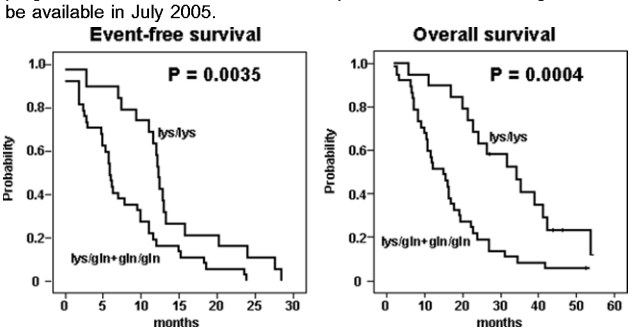
Background: It has been shown that Xeroderma pigmentosum complementation group D protein (XPD), an essential member of the Nucleotide Excision Repair pathway, plays a major role in the efficacy of platinum derivatives. A single nucleotide polymorphism (SNP), leading to a Lys>Gln change at position 751 of the protein, is accompanied by a survival disadvantage in patients treated with 5-fluorouracil-oxaliplatin (FolFOx) for metastatic colorectal carcinoma [1]. It is not clear however whether this SNP predicts for survival independently from treatment (prognostic factor) or is a true marker predicting for oxaliplatin efficiency.
Patients and Methods: 56 patients treated in first-line chemotherapy with FolFOx regimen and 54 similar patients treated with 5-fluorouracil-irinotecan (FolFIri) regimen have been retrospectively included. DNA was extracted from non-tumoral tissue embedded in paraffin blocks obtained from the pathology archives and XPD genotypes were identified by PCR and restriction fragment length analysis. Treatment response, event-free survival and overall survival were recorded.
Results: In the FolFOx group, genotype prevalence was Lys/Lys 34% (19 patients), Lys/Gln 55% (31 patients), Gln/Gln 11% (6 patients). Patient survival was significantly correlated to the presence of the SNP: event-free survival and overall survival were respectively, for patients having at least one variant allele, 6 months and 15 months, while the figures were 12 months and 34 months for common homozygous patients ($P = 0.0035$ for event-free survival and 0.0004 for overall survival, see figure). In multivariate analysis, the XPD genotype appeared as the most significant prognostic factor. The results for the 54 patients of the FolFIri regimen will be available in July 2005.



Conclusion: The Lys751Gln XPD polymorphism influences, in univariate and multivariate analyses, the event-free and overall survivals in metastatic colorectal cancer treated with first line chemotherapy consisting of 5-fluorouracil-oxaliplatin combination. Determining the impact of the polymorphism in patients treated in the same situation by a 5-fluorouracil-irinotecan combination will allow to conclude whether this polymorphism is a prognostic factor or a marker of oxaliplatin activity.

References

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