9025 POSTER

Expression of cyclooxygenase-2 in cytological material from patients with lung cancer

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Background: Cyclooxygenase-2 (COX-2)-expression may be predictive for the effect of celecoxib in patients with advanced non-small cell lung cancer (NSCLC). In previous studies, COX-2-expression has almost exclusively been evaluated with immunohistochemical methods performed on histology sections of tissue biopsies. However, in clinical practice, lung cancer is often diagnosed with cytological techniques only. Methodology and results from analysis of COX-2-expression in cytological material from lung cancer patients by immunocytochemistry have, to our knowledge, not been described previously.
Material and Methods: Fifty-three patients with lung cancer were prospectively examined. Material was obtained from routine diagnostic transbronchial fine-needle aspirations or transthoracic needle aspiration. Slides with obvious tumour cells were selected, fixed in 4% paraformaldehyde and immunostained with monoclonal antibody mouse-anti-human COX-2. An experienced cytopathologist evaluated the slides as well as routinely stained parallel slides. Percentage stained tumour cells (<1%, 1−10%, 11−50%, >50%) and intensity of staining (none, weak, strong) were estimated. Clinical data were collected from patient records.
Results: There were 32 men and 21 women with median age 68 years (range 43−87). Eighty-nine percent had NSCLC. Preparation and staining with the methods established at our laboratory were easy to perform. Quality and readability of the slides were generally good. Tumour cells, singly and in clusters, were easily discriminated from benign cells. The percentage COX-2-stained cells and the intensity of staining varied widely between and within the different cases. The proportion of positively stained tumour cells was as follows: <1%: 20 pts., 1−10%: 7 pts., 11−50%: 17 pts., more than 50%: 9 pts. In 17 cases, groups of cells with different intensity of COX-2-staining were found in the same slide. There were no significant differences in survival when grouping the cases according to percentage of COX-2-expression.
Conclusions: Immunocytochemical analysis of COX-2-expression is technically easy to perform with routine diagnostic procedures resulting in easily readable, high quality slides. There is a great variation in the proportion of COX-2-positive cells from case to case as well as in the intensity of staining between individual cells in many single cases.

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The prognostic significance of [18F]flurodeoxyglucose uptake by positron emission tomography in advanced non small cell lung cancer

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Background: Lung cancer is the leading cause of cancer-related death in Korea. Non small cell lung cancer(NSCLC) comprises 80−85% of lung cancer. Positron emission tomography with [18F]fluorodeoxyglucose(FDG-PET) shows various levels of FDG uptake for patients with NSCLC. The aims of this study were to determine whether the standardized uptake value (SUV) of FDG uptake by PET could be a prognostic factor for advanced NSCLC.
Method: FDG-PET was performed for 59 patients with stage IIIb and IV non small cell lung cancer. The SUV was calculated for each patient. Overall survival(OS), progression free survival(PFS) were calculated by the Kaplan- Meier method and evaluated with the log-rank test. The prognostic significance was assessed by univariate and multivatiate analysis.
Results: A cutoff of 7 for the SUV showed the best criminative value. In a univariate analysis, performance status($p = 0.02$) and SUV($p = 0.03$) were the significant predictors of OS. The patients with low SUVs($\leqslant 7$) showed significantly better PFS than those with high SUVs(>7, $p = 0.04$). A multivariate Cox analysis identified performance status and the SUV as important for the prognosis.
Conclusion: These results suggest that SUV was the significant prognostic factor among the patients with advanced non small cell lung cancer.

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Patient-derived tumourgrafts of non-small cell lung cancer (NSCLC) as models for the identification of predictive biomarkers for classical and targeted therapies

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Background: With the newly developed tyrosine kinase inhibitors drugs are available for the targeted treatment of patients with NSCLC. But clinical trials revealed no clear correlation between the EGFR expression and the response to targeted therapy. Several aspects concerning the individual prediction of response (mutations, expression levels) have been investigated but did so far not result in the acceptance of a routine biomarker for clinical use. Therefore, we intended to use a novel xenotransplantation system for the investigation of clinically relevant biomarkers.
Material and Methods: We have developed a series of novel lung cancer tumorgrafts. Fresh tumor material of patients with NSCLC was subcutaneously transplanted to immunodeficient mice shortly after removal. 25 passagable models could be generated and were used for the definition of predictive biomarkers and concerning the responsiveness to classical (Paclitaxel, Gemcitabine, Carboplatin, Vinorelbine, Etoposide) or targeted (Cetuximab, Erlotinib) therapies.
Results: It was demonstrated that the early murine passages correlated with the original tumor regarding histology, the expression of the surface proteins and in gene profiling (Affymetrix).
12/25 tumorgrafts were sensitive towards Cetuximab and 6/25 towards Erlotinib. None of the tumorgrafts showed functional mutations in the EGFR gene. 5/25 models with K-ras mutations were found among the xenografts; four of these tumors were resistant towards Erlotinib. In 12/25 different models mutations in the p53 gene could be located. All xenografts are Met wt and only two revealed PI3K mutations. None of these mutations was clearly correlated with a specific response towards anti-EGFR therapies. 23/25 tumors were positive for E-cadherin and 7/25 for Vimentin suggesting that the potential for epidermal-mesenchymal transition is not directly correlated with any therapeutic response. But in a few sensitive tumors a translocation of E-cadherin into the nucleus was found after Erlotinib treatment. The expression of EGFR ligands like TGFalpha and epiregulin was weakly correlated with the response to Erlotinib or Cetuximab.
Conclusions: In summary, we have established a panel of well characterized NSCLC tumorgrafts. These models better represent the heterogeneity of lung cancer, correlate with the clinical situation and are able to identify biomarkers and their regulation after therapeutic interventions both at genetic and at protein level.

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Genetic polymorphisms of the endothelial nitric oxide synthase gene correlate with overall survival in advanced non-small-cell lung cancer treated with platinum-based doublet chemotherapy

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Background: Nitric oxide (NO) is a small free radical that is involved in carcinogenesis. Endothelial NO, synthesized from L-arginine by endothelial NO synthase (eNOS), inhibits apoptosis and promotes angiogenesis, tumor cell proliferation and metastasis. The aim of this study was to evaluate the influence of eNOS gene polymorphisms on the prognosis of patients with advanced-stage non-small-cell lung cancer (NSCLC).
Patients and Methods: Unresectable, chemotherapy naïve stage III or IV NSCLC patients treated with a standard platinum-containing doublet regimen were analyzed. All individuals were genotyped for a single-nucleotide polymorphism (SNP), 894 G to T in exon 7, and a variable number of tandem repeats (VNTR) polymorphism in intron 4, a rare smaller allele (a) and a common larger allele (b), to elucidate a potential association between these polymorphisms and clinical outcome.
Results: From July 2004 to July 2007, a total of 108 patients (male/female: 66/42, PS 0/1 = 23/85, Stage IIIA/IIIB/IV = 6/30/72), aged 29−77 (Median: 63) years, were consecutively enrolled in this study. Definite thoracic radiotherapy was administered in 20 (18.5%) patients. The median survival was 26.8 months. Using Kaplan-Meier estimates to calculate 5-year probabilities of follow-up, we could show that overall survival