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1097 POSTER

Genetic polymorphisms of thymidylate synthase and DNA repair genes are associated with the toxicities of S-1 and cisplatin combination chemotherapy in metastatic or relapsed biliary tract cancer

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Background: Biliary tract cancers (BTC) are often diagnosed at advanced stage and are still fatal in the majority of patients. Although the standard chemotherapy for metastatic or relapsed BTC is not established yet, we recently reported phase II trial which showed the efficacy of S-1 and cisplatin combination chemotherapy (Kim et al. Ann Oncol, 2008). In addition, it was suggested that genetic polymorphisms, especially genes related to 5-fluorouracil and cisplatin activity, may be associated with various toxicities of chemotherapy.
Objective: The aim of this study was to explore the relationship between the toxicity of S-1/cisplatin combination chemotherapy and the germline polymorphisms of genes associated with these agents including thymidylate synthase (TS), xeroderma pigmentosum group D (XPD), the excision repair cross-complementation 1 (ERCC1), and X-ray repair cross-complementing group (XRCC).
Methods: Ninety-four patients were received S-1 80 mg/m^2 day 1−14 and cisplatin 60 mg/m^2 on day 1 every 3 weeks. Genomic DNA was extracted from the mononuclear cells obtained from the patients before receiving S-1 and cisplatin. Polymorphisms were analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.
Results: Median follow up duration was 22 months (95% Confidential Interval (CI): 11.1−22.9 months). Objective response rate was 33.4%. Median progression-free and overall survival were 5 and 9 months, respectively (95% CI: 1.2−5.8 and 7.1−10.9 months, respectively). Diarrhea was significantly more frequent in patients possessing TS 3'-untranslated region (UTR) 6bp deletion homozygote (42.6% in −6bp/−6bp vs. 20% in +6/−6 or +6/+6, *P = 0.021*). Grade 3−4 anemia was more frequently observed in patients with TS 3'-UTR 6bp deletion homozygote (20.4% in −6bp/−6bp vs. 5% in +6/−6 or +6/+6, *P = 0.038*). The C/C genotype of XPD-Arg156Agr was significantly associated with grade 3−4 neutropenia (50% in the C/C genotype vs. 23.5% in the C/A or A/A genotype, *P = 0.013*). The C/T or T/T genotype of XRCC1-Arg194Trp, the G/G genotype of XRCC1-Arg399Gln, and the C/C genotype of ERCC1-C8092A were significantly correlated with grade 3−4 thrombocytopenia (*P = 0.045*, *P = 0.039*, and *P = 0.037*, respectively).
Conclusion: Our results suggest that germline genetic polymorphisms in TS and DNA repair genes are associated with increased risk of toxicities in BTC patients who received S-1 and cisplatin combination chemotherapy.

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Influence of IL-4 −590C/T polymorphism in Non-Small Cell Lung Cancer (NSCLC) susceptibility

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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). Inflammation and related pathways play an important role in the pathogenesis of lung cancer. IL-4 is an anti-inflammatory cytokine, which reduces the production of proinflammatory cytokines by monocytes and with direct antiproliferative effects in some tumors. The polymorphism *−590 C/T* SNP is a C to T transition in the *−590* position of the promoter region of the *IL-4* gene, and the T variant is associated with increased expression of IL-4. The aim of this study was to evaluate the influence of this polymorphism in the susceptibility to non-small cell lung cancer development (NSCLC).
Methods: DNA was extracted from peripheral blood of 696 individuals (277 patients diagnosed with NSCLC and a control group of 419 individuals without cancer). The characterization *IL-4 −590C/T* genotypes was performed by PCR-RFLP (*BsmFI*).
Results: The *−590 C/T* polymorphism genotypes were classified as low (CC) and high expression (TT). The frequencies obtained for the CC and TT genotypes were 86.3% and 13.7%, respectively, in the control group and 92.3% and 7.7%, respectively, in the case group. The analysis of the TT and CC genotype frequencies in the two groups under study showed a statistically significant difference in its distribution, indicating a protection of 48% for the development of NSCLC in individuals with the TT genotype when compared with individuals with CC genotype (P = 0.036, OR = 0.522: 95% CI = 0.282−0.965). This result is more pronounced when considering only the NSCLC epidermoid histological type (P = 0.003, OR = 0.086: 95% CI = 0.012−0.636). Stratifying according to smoking status, the results also show that smokers with the TT genotype have a protection for the development of NSCLC (P = 0.007, OR = 0.100: 95% CI = 0.013−0.772), when compared with the non-smoking group with TT genotype.
Conclusion: The results of this study point to the involvement of CC and TT genetic variants of the *IL-4 −590 C/T* polymorphism in the development of NSCLC. Increased expression of IL-4 associated with the TT genotype may contribute to the promotion of immune surveillance during NSCLC development, which could explain the results obtained in this work. However, further functional studies regarding IL-4 expression according to *IL-4 −590 C/T* polymorphism genotypes should be conducted in order to validate this hypothesis.

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Influence of CXCR4 localization on in vitro migration of non small cell lung cancer cell lines and on clinical outcome in NSCLC

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Background: Metastatic spread is the primary source of morbidity and mortality in non-small cell lung cancer (NSCLC). CXCR4, a G protein coupled chemokine receptor, and its ligand, stromal cell derived factor-1 (SDF-1), play a critical role in organ specific tumor metastasis. In vitro, CXCR4 expression has been shown to correlate with migration, invasion and adhesion. In vivo, patients whose tumors exhibit high CXCR4 expression have a poorer clinical outcome, while nuclear localization of the receptor specifically confers a better prognosis. We investigated the effect of CXCR4 localization on NSCLC cell migration and set out to quantify the expression of CXCR4 on tumor specimens from NSCLC patients to correlate CXCR4 localization with clinical outcome.
Methodology: CXCR4 localization was determined by cell fractionation and western blot, immunocytochemistry (IHC) and flow cytometry. Migration was investigated using a 48-well Boyden chamber. Demographic details, clinical variables and outcome data were gathered on patients diagnosed at the TBCC in 2004–2005. Formalin-fixed paraffin embedded tumor specimens (resected tumors Stage I and II; biopsies stage IV) were obtained and tissue micro arrays (TMA's) generated. CXCR4 expression was analyzed within lung cancer cells using the HistoRx PM-2000 platform. Statistical analysis was by Kaplan-Meier method, multivariate analysis and spearman's rank correlation.
Results: Inhibition of the this axis reduced cell migration. The degree of inhibition correlated with membrane localization of CXCR4. 790 patients were diagnosed with NSCLC at the TBCC in 2004–2005; 390 stage IV disease with 170 tissue samples available, 80 suitable for TMA generation; 85 early stage resected disease, all with suitable tissue. Preliminary analysis showed that the stage-based overall survival parallels results seen in other studies. The overall survival of patients whose tumors were suitable for TMA generation did not differ from the general cohort. Automated IHC for CXCR4 was successfully completed in all TMAs.
Conclusions: In vitro interruption of the CXCR4/SDF-1 axis inhibits the migration of NSCLC cells and correlates to membrane localization of CXCR4. Although the proportion of patients whose tissue is suitable for TMA generation makes up only 25−30% of all stage IV patients, this does not seem to introduce outcome bias in our cohort. CXCR4 expression is expressed in a large proportion of NSCLC tumors. Final results on the relationship between CXCR4 expression and outcome will be presented.

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Peripheral blood lymphocite populations in advanced gastric cancer patients have predictive and prognostic value

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Introduction and Objectives: Quantify in gastric cancer patients peripheral blood lymphocite populations levels at diagnosis time and their value as a treatment response predictor and as a survival prognostic factor.
Patients and Methods: Were eligible for this study irresectable/locally advanced and metastatic gastric cancer patients. Relapsed gastric cancer patients after radiacal surgical treatment were also eligible. No surgical,