Conclusions: Judging from the results of our retrospective study, p53 is related to disease progression but is uncertain as prognostic factor in GISTs. We think that tumor size, mitotic rate and elevated Ki67 index is the helpful prognostic factors in GISTs.

763 POSTER

Prediction of chemosensitivity to 5-FU in gastric cancer by gene polymorphism

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Background: Fluorouracil is widely used in the treatment of gastric cancer. Thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD) and methylenetetrahydrofolate reductase (MTHFR) relate with the action of 5-FU. The aim of this study was to evaluate the predictive value of gene polymorphism of these enzymes to the effect of 5-FU in patients with gastric cancer by HDRA (histoculture drug response assay).
Material and methods: From August 2004 to April 2005 we examined eighty-seven histologically proven gastric carcinoma tissue specimens with HDRA to 5-FU. Patients were categorized into a chemosensitive (>30% inhibition) or chemoresistant (30% inhibition >) group. All patients were received postoperative adjuvant immunochemotherapy with mitomycin, 5-FU and OK-432. Genomic DNA was extracted from blood and genotypes were determined.
Results: There were no significant relationships between chemosensitivity and gene polymorphisms (TYMS gene polymorphisms (double (2R) or tri-tandem (3R) repeats of a 28-bp sequence in the promoter region ($p = 0.34$) and a 6-bp variation in the 3'-untranslated region ($p = 0.15$)) and MTHFR C677T polymorphism ($p = 0.18$)). IVS14 + 1G>A mutation in the dihydropyrimidine dehydrogenase gene was not noted in all patients.
Conclusions: Our data did not provide evidence that gene polymorphism of these enzymes influence the effect of 5-FU in patients with gastric cancer. But the observation of these patients can provide additional information of relationships between clinical data and gene polymorphisms.

764 POSTER

A novel mode of antitumor activity for imatinib mesylate: consequences for the design of surrogate markers of efficacy and combination therapies

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We have recently reported that STI571 has not only a tumor cell autonomous effect but also acts on host dendritic cells (DC) to promote natural killer (NK) cell activation and NK cell-dependent antitumor effects in mice (Borg C. et al, J Clin Invest, 2004).
Moreover, about 50% of gastrointestinal sarcoma (GIST) bearing patients undergoing therapy with STI571 acquire NK cell activation correlating with clinical outcome. The study of the Time To Progression (TTP) for 43 patients that benefited from a median follow up of 13.2 months in both cohorts of GIST, those exhibited enhanced NK cell functions ($n = 22$) at 2 months of Gleevec versus those who did not ($n = 21$) revealed that TTP is significantly longer in patients with NK cell activation (Log Rank Test, $p = 0.03$).
The potential associated prognostic factors: type of c-kit mutation, extra-gastric primary tumor, haemoglobin level <7 g/dL, performance status over 2 and pulmonary metastases at entry, were all comparable in these two cohorts.
The lack of STI571-mediated NK cell induction found in the other 50% of cases could be assigned to the presence of high numbers of $CD4^+CD25^{high}$ regulatory T cells (Treg) in blood at entry, which were shown, by us, to inhibit NK cell effector functions in human ex-vivo and in-vitro. The mean percentages of Treg among $CD3^+CD4^+$ T cells in GIST patients displaying NK cell induction were not elevated compared with normal volunteers (mean 1.1 ± 0.3 GIST, mean 1.2 ± 0.4 in NV, $p = 0.5$) whereas these yields were increased by three fold in the group of patients with no NK cell induction (mean 3.2 ± 0.8E in GIST, $p = 0.02$). We finally found that the combination of immunopotentiating dosages of cyclophosphamide (aimed at reducing Treg function) with STI571 had synergistic anti-tumor effects in a mouse model of lung melanoma metastases. Altogether, NK cell activation is a novel surrogate marker of efficacy of STI571 which is critical for TTP and could be enhanced by pre-treatment of GIST patients with Treg inhibitors.

765 POSTER

Influence of hepatic dysfunction on safety, tolerability, and pharmacokinetics of PTK/ZK in patients with unresectable hepatocellular carcinoma

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Background: Vascular endothelial growth factors (VEGFs) and VEGF receptors (VEGFRs) are important mediators of tumor growth and metastasis, and their expression is associated with poor prognosis in patients (pts) with hepatocellular carcinoma (HCC). PTK/ZK is a novel, oral, angiogenesis and lymphangiogenesis inhibitor that blocks tyrosine kinase signaling from all known VEGFRs.
Methods: This was an open-label, multi-center, phase I study to characterize the safety, tolerability, and pharmacokinetic (PK) profile of PTK/ZK, administered once daily at a dose of 750 mg, 1,000 mg, or 1250 mg in adults with unresectable HCC. Pts previously treated with surgery, chemotherapy, or radiotherapy were eligible. Pts were stratified into 3 groups based on total bilirubin and AST/ALT levels. Pts in groups 1–3 had mild, moderate, and severe hepatic dysfunction, respectively. PK data were collected from all pts on days 1, 28, and 56. The primary endpoints were safety, tolerability of PTK/ZK, and the effects of hepatic dysfunction on the PK of PTK/ZK.
Results: 34 pts were enrolled, 21 in group 1; 8 in group 2; and 5 in group 3. In all groups, the most frequently reported adverse events (AEs) were nausea, vomiting, anorexia, fatigue, diarrhea, and dizziness. A correlation between these AEs and the study drug dose was not observed. In group 1, 2 of 4 pts who received the 1,250 mg/d dose experienced unacceptable AEs (Common Toxicity Criteria [CTC] grade 3 fatigue and CTC grade 4 elevation of AST). 2 of the 6 pts who received the 1,000 mg/d dose experienced unacceptable AEs (ALT over 1.5 x baseline and fatal hepatic tumor hemorrhage). No unacceptable AEs were observed at the 750 mg/d dose, defined as the maximum tolerated dose in pts who have mild hepatic impairment. PK analysis indicated that there was no accumulation of PTK/ZK. Patients' time on PTK/ZK treatment ranged from 5 to 415 days. The best response based on modified RECIST criteria was stable disease. There were no partial responses or complete responses.
Conclusion: PTK/ZK is generally well tolerated in most pts with mild and moderate degrees of HCC-related hepatic impairment at the dose of 750 mg/day.

766 POSTER

Prominent tumour-infiltrating lymphocites improved disease free survival in early stage gastric carcinoma

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Introduction: The degree of lymphocytes infiltration is a significant determinant of outcome for a variety of malignancies including non Hodgkin's lymphoma, oesophageal carcinoma, malignant melanoma, colorectal carcinoma and breast cancer. Pathologists have for a long time recognised that tumour prognosis is closely correlated with several morphological features including histological type, TILs, tumour associated eosinophils and mast cell. Gastric cancer could be associated with lymphocytic infiltrate, although the functional role and prognostic significance of this infiltrate is unknown.
Materials and methods: Patients: Between 1993 and 2004, 204 patients underwent a R0 gastric resection for T1-T2 N0. 55 of these patients (31 men and 24 women with a mean age of 62.82 ± 11.8) were analysed. Correlation between free disease survival and clinical (age, sex), and pathological features (tumour site and diameter, Laurén, Bormann and WHO classification, vascular and lymphatic invasion, pTNM) were analysed.
Histopathological examinations: All surgical specimens stained with haematoxylin and eosin (H&E). Microscopic examination included histological differentiation of tumour, assessment of invasion, identification of presence of cancer cells at the surgical margin and IEL, PLT and CRL (Figure 1) infiltrating lymphocytes.
Statistical analysis: Software SPSS 11.0 was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Correlations of clinic pathological features and molecular alterations gastric and disease free survival cancers were analysed using the Cox regression. Overall disease free survival was