We are sure that type of mutation significantly influenced GIST prognosis and mutations should be analyzed before adjuvant therapy.

6607 POSTER

Description of Mutation in CNR1 Gene and VEGF Expression in Esophageal Cancer

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Aims and Background: Cannabinoid receptors have an impact on gastrointestinal function, but it remains unknown whether mutations may affect tumour susceptibility in patients with esophageal carcinoma. The aim of this study was to determine mutation in the cannabinoid receptor-1 (CNR1) gene and its relation to vascular endothelial growth factor (VEGF) expression as an angiogenic and poor prognostic factor.
Methods: 179 esophageal tissue samples from 69 patients (29 with esophageal cancer and 40 controls) were studied. CNR1 gene mutation (1359 G $\rightarrow$ A in codon 453) was detected with PCR, using the MspI restriction enzyme. VEGF was determined by immunoassay.
Results: Genotyping in control patients' samples revealed that 24/40 were G/G wild type and 16/40 were G/A; no samples were A/A. Of the 139 tissue samples from the 29 esophageal cancer patients, 15 were G/G homozygous, 85 G/A heterozygous, 11 had an A/A genotype and 28 were without amplification. In the normal tissue adjacent to tumour, some mutations were observed. The overall survival time was reduced in patients with the A/A type in all their 5 samples, in comparison to G/G type ($P = 0.04$, chi-square: 4.26). VEGF expression was higher in tumour than nontumour areas ($P < 0.025$). VEGF expression was not correlated with survival time.
Conclusions: Our preliminary findings in esophageal tissue showed a high frequency of G $\rightarrow$ A mutation in the CNR1 gene. No correlation between VEGF expression and gene receptor mutation was found. Patients with mutation in all their samples had a reduced survival time.

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Bax and p53 as Outcome Predictive in Metastatic Gastric Cancer (MGC) Patients Treated With First-Line COI (Capecitabine, Oxaliplatin, and Irinotecan) Regimen

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Background: Bax plays a central role in apoptosis signalling and might be a chemosensitivity biomarker. P53 is a gene regulator of Bax, but its significativity as independent biomarker is controversial. Poorer survival for localised tumours harbouring double alteration of Bax and p53 was previously reported, although only Bax was an independent prognosticator *(Mrózek, 2003*). The aim of this retrospective study was to investigate the predictive/prognostic value of Bax/p53 in mGC pts homogeneously treated with a oxaliplatin-containing regimen.
Methods: First-line treatment with COI (capecitabine 1000 mg/m^2 twice daily d2−6; oxaliplatin 85 mg/m^2 d2; irinotecan 180 mg/m^2 d1; biweekly schedule) was administered to a consecutive series of mGC pts for up to 8 cycles, or until progressive disease (PD)/unacceptable toxicity. Performance status (PS) $\leqslant 1$: eligibility criteria to triplet chemotherapy. Tissue blocks available for 23 pts who provided written consent. Bax/p53 expression assessed by immunohistochemistry, with dicotomic discrimination. Association of both biomarkers with RECIST response by two tailed Fisher's exact test. Correlation of Bax/p53 and PS with progression-free (PFS) and overall (OS) survival by univariate and multivariate Cox's proportional hazard model.
Results: Two pts not evaluable by RECIST criteria. Overall, 71% response rate (15/21, 11 PR/4 CR). Bax-positive was documented in 74% (17/23) samples and negative in 26% (6/23); p53 negative in 61% (14/23) and overexpressed in 39% (9/23). Response rate was 87% (13/15) in Bax-positive and 33% (2/6) in BAX-negative ($p = 0.03$). By Cox univariate analysis, Bax negative tumours showed a statistically significant shorter PFS (3.9 vs 7.4 mos; HR = 3.40, CI 1.17–9.93; $p = 0.02$) and OS ($p = 0.04$). In multivariate analysis for Bax and PS, Bax-negative tumours showed a significantly higher risk for progression (HR 4.51, CI 1.30–15.6; $p = 0.02$) and death (HR 6.69, CI 1.30–15.6; $p = 0.01$); and sub-optimal PS (ECOG 1) was associated with a trend for worst overall survival ($p = 0.08$). p53 evaluation failed to show any significant correlation with outcome.
Conclusions: In mGC pts selected for good-intermediate PS, Bax expression is associated with higher responses to first-line COI regimen. Bax negative pts showed poorer outcome, while p53 overexpression did not have an impact on disease prognosis. Prospective confirmation of predictive/prognostic role of Bax in mGC treated with specific chemotherapeutic drugs is warranted.

6609 POSTER

RON (MST1R) is a Novel Therapeutic Target for Gastroesophageal Adenocarcinoma

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Background: RON (MST1R) is a member of the MET receptor tyrosine kinase family with a putative role in cancer, and we have recently described its expression and function in human tissues and *in vitro* in gastroesophageal cancer (GEC) (AACR 2011, LB-124, Catenacci et al; in press); here we further describe the role of RON expression and therapeutic potential in a murine model, with focus on RON and MET signaling synergy and redundancy as a mechanism of resistance to individual receptor inhibition.
Methods: To confirm our *in vitro* findings, we assessed the function of RON in a GEC cell line, AGS, in a subcutaneous nude mouse model. GEC cell line growth inhibition was evaluated using RON specific novel monoclonal blocking antibodies, small molecule tyrosine kinase inhibitors and a RON shRNA AGS line. We used immunohistochemistry (IHC), immunoblotting (IB), and fluorescence in situ hybridization (FISH) to evaluate RON and MET expression, activation, and copy number in harvested treated tumours and controls to evaluate for mechanisms of resistance. We assessed RON and/or MET inhibition in order to evaluate for inhibitory synergism as a result of RON and MET functional reciprocity and signaling redundancy as we recently described *in vitro*.
Results: Tumour take rate was significantly inhibited with RON knockdown in the shRON AGS line versus scrambled control ($p < 0.01$). Those shRON tumours that did take occurred significantly later than control − with some revealing increased MET expression and others through selection of a RON re-expressing clone. shRON tumours were significantly less vascular as assessed grossly and by anti-CD31 IHC. shRON tumour growth rate was significantly less than the scrambled AGS control ($p < 0.01$). RON and MET simultaneous inhibition with monoclonal antibodies or small molecules resulted in a lower tumour take rate and growth rate than with inhibition of either receptor alone or negative controls.
Conclusions: RON protein knockdown and inhibition with antibodies and small molecules significantly decreased the ability of tumours to take, with less tumour vasculature providing a possible downstream mechanism of action. This suggests a role for neoadjuvant/adjuvant anti-RON treatment of GEC in the peri-operative setting to improve disease-free survival, as well as in the advanced metastatic setting given the observed tumour growth inhibition. RON and MET co-inhibition led to optimal results, confirming our previous *in vitro* observations. These studies further define RON as an important novel therapeutic target for GEC, and supports continued investigation of its role and development of RON specific inhibitors for this deadly disease.

6610 POSTER

The Significance of the Changing of Serum M30 and M65 Values After Chemotherapy and Relationship Between These Values and Clinicopathological Factors in Patients With Advanced Gastric Cancer

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Background: M30 and M65 are intact forms of cytokeratin 18 and, they release during apoptotic cell death from the epithelial cells. In some studies, prognostic importance and predictive significance to detect response to chemotherapy of M30 and M65 values have been reported. In the present study, we aimed to determine the changing of serum M30 and M65 values after chemotherapy and the impact of these values on treatment response and progression-free (PFS) and overall survival (OS) of patients with advanced gastric cancer.
Material and Methods: A total of thirty-one patients with advanced gastric cancer were included. M30 and M65 values were measured by quantitative ELISA method in serum samples before and 48 hours after first chemotherapy cycle. Pre- and postchemotherapy values of M30 and