in Mf, 59 in iceMFP) were excluded because of postoperative stage I in 90, IV (M1) in 13, positive resection margin in 10, and others in 6. Therefore, a total of 521 pts (258 in Mf, 263 in iceMFP) were eligible for intent-to-treat analysis. Postoperative stages were II in 33.4%, IIIA in 31.9%, IIIB in 17.5%, and IV in 17.3% of pts. With a median follow-up of 6.6 years, a total of 271 events (relapse or death) have been observed. As compared with Mf group, iceMFP group had a higher likelihood of relapse free survival (RFS) (HR, 0.73; 95% C.I. 0.57–0.93; p = 0.0092; 5yRFSR 53.9% vs 46.3%) and of overall survival (OS) (HR, 0.77; 95% C.I. 0.60–0.98; p = 0.0365; 5yOSR 59.2% vs 50.3%).
Conclusions: Considering no benefit of adding cisplatin and prolongation of oral doxifluridine to Mf chemotherapy in curatively resected AGC pts (AMC0201), intraperitoneal cisplatin and/or early start of chemotherapy seemed to be responsible for the improved efficacy of iceMFP chemotherapy in this study.

Poster Presentations (Mon, 26 Sep, 09:30−12:00) **Gastrointestinal Malignancies − Noncolorectal Cancer**

6506 POSTER

Tricellulin Expression in Normal and Tumorous Human Pancreas

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Background: Tricellulin (TRIC) is the first identified member of transmembrane tight junction (TJ) proteins, found concentrated mainly at tricellular contacts. However, together with occludin and claudins it can also be detected at bicellular junctions. TJs play essential role in cell adhesion as well as in the maintenance of paracellular barrier and are also involved in signal transduction. Further, altered expression of several TJ components was observed during carcinogenesis and tumour progression. Previously, our group described significant differences between exocrine and endocrine pancreatic tumours related to claudin expression. The aim of the present study was to analyze the expression and localization of TRIC in normal human pancreas as well as in exocrine and endocrine primary tumours of the pancreas.
Materials and Methods: A total of 82 cases were studied: 20 normal pancreas, 44 ductal adenocarcinomas (PDACs) (grade 1−3), 15 endocrine neoplasms (PENs) and 3 acinar cell carcinomas (ACCs). Fluorescent microscopic examination and Western-blot analysis were performed on fresh frozen samples, immunohistochemical analysis and RT-PCR on formalin-fixed, paraffin embedded materials. Data were analyzed by digital morphometry and evaluated statistically.
Results: TRIC was found apically localized in normal ducts and acini. Intensive, spotty immunopositivity was detected at tricellular contacts, while weaker signals were observed between two cells. Langerhans islets were negative. The appearance of TRIC in PDACs, however, was unorganized as compared with normal tissue. Well differentiated PDACs expressed TRIC at significantly higher levels compared with poorly differentiated adenocarcinomas. Kaplan-Meyer analysis showed significant correlation between survival and differentiation of PDACs and inverse correlation with TRIC expression. ACCs expressed TRIC in atypical, abortive acinar cells. All PENs were TRIC negative.
In conclusion, this is the first report to describe the TRIC expression profile in normal and neoplastic human pancreas. Both normal and tumorous pancreatic exocrine tissues expressed TRIC, whereas no expression was notable in the normal and tumorous endocrine cells. Further, TRIC expression in PDACs revealed significant negative correlation with the degree of differentiation and survival.
This project was supported by grant # OTKA 75468 and TAMOP.4.2.1.B-09/1/KMR-2010–0001.

6507 POSTER

Effects of the Proteasome Inhibitor Bortezomib Alone and in Combination With Chemotherapeutic Agents in Gastric Cancer Cell Lines

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The proteasome plays a pivotal role in controlling cell proliferation, apoptosis, and differentiation in a variety of tumour cells. Bortezomib is a boronic acid dipeptide derivative, which is a selective and potent inhibitor of the proteasome and has prominent effects in vitro and in vivo against several solid tumours. We examined the anti-proliferative and apoptotic effects of bortezomib in three gastric cancer cell lines (SNU638, MUGC-3 and MKN-28), along with its antitumour combination effects with other chemotherapeutic agents.
Tumour cell growth inhibition and apoptosis was measured by MTT assay and FACS analysis, respectively. Apoptosis- and cell cycle-associated protein expression levels were measured by Western blot assay. Bortezomib induced the suppression of tumour cell growth and apoptosis in a dose-dependent manner with an inhibitory dose (ID)50 of approximately 0.5 μg/ml in all gastric cancer cell lines tested. Further combination treatment with cisplatin and docetaxel, in particular with docetaxel displayed dramatically increased tumour cell growth suppression in all three gastric cancer cell lines, as compared to single drug treatment alone. This was concomitant with the induction patterns of apoptotic cells. Bortezomib treatment increased the Bax protein expression. Moreover, combination treatment of bortezomib plus docetaxel resulted in a dramatic increase in the Bax expression. In contrast, Bcl-2 expression was decreased by combination treatment with bortezomib plus docetaxel in SNU638 cells. Finally, bortezomib, docetaxel and to a greater degree bortezomib plus docetaxel increased the expression levels of p27 proteins even without influencing p53 expression levels. Bortezomib has profound effects on tumour cell growth inhibition and induction of apoptosis in human gastric cancer cells, suggesting that bortezomib may be an effective therapeutic drug for patients with gastric cancer. Further combination studies with other chemotherapeutic drugs, in particular docetaxel showing more tumour cell growth inhibition and apoptosis suggest that combining bortezomib with docetaxel might be more effective for displaying tumour cell growth inhibitory effects in gastric cancer cells through regulation of Bcl-2, Bax and p27 proteins in vitro.

6508 POSTER

A Case–control Study on the Effect of Apolipoprotein E Genotype on Gastric Cancer Risk and Progression

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Background: Apolipoprotein E (ApoE) is a multifunctional protein playing a key role in the metabolism of cholesterol and triglycerides as it mediates blood clearance of cholesterol-rich particles. ApoE gene (19q13.2) has three major isoforms encoded by ε2, ε3 and ε4 alleles with the ε4 allele associated with hypercholesterolemia and the ε2 allele with the opposite effect. An inverse relationship between cholesterol levels and gastric cancer (GC) has been previously reported, although the relationship between ApoE genotypes and GC has not been explored to date.
Since the question on the role of hypocholesterolemia as a predisposing factor, or result of the preclinical stage of GC itself, remains still under debate, our hospital-based case-control study aimed to overcome this issue by directly looking at the relationship between ApoE genotypes and GC, as well as the interaction with potential effect modifiers.
Materials and Methods: One hundred and fifty-six gastric cancer cases and 444 hospital controls were genotyped for *apoE* polymorphism. The relationship between GC and putative risk factors was measured using the adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. A gene-environment interaction analysis was performed.

Table: Distribution of *ApoE* polymorphism among gastric cancer cases and controls

	Cases n (%)	Controls n (%)	OR (95% CI)[†]
ε3/ε3	109 (71.71)	253 (62.94)	1*
ε3/ε2 or ε2/ε2	15 (12.10)	68 (21.18)	0.40 (0.19–0.84)
ε3/ε4 or ε4/ε4	27 (19.85)	76 (23.10)	0.68 (0.36–1.26)

[†]OR adjusted by age, gender, alcohol consumption (as continuous variable), packyears of smoking, grilled meat consumption and familiy history of gastric cancer. *Reference category.

Results: Alcohol consumption was associated with an increased GC risk with ORs of 1.84 (95% CI = 1.10–3.07) and 3.29 (95% CI = 1.36–7.98) for moderate and heavy drinkers, respectively. A nearly doubled GC risk (OR = 1.95, 95% CI: 1.06–3.60) was detected among individuals smoking more than 25 pack-years. As shown in the table, a statistically significant 60% decreased GC risk (OR = 0.40, 95% CI: 0.19–0.84) was observed for those carrying at least one *apoE* ε2 allele if compared with

ε3 homozygotes while no effect was shown for ε4 allele carriers. No statistically significant interaction emerged between the ε4 or ε2 allele and environmental exposures. In addition, ε2 or ε4 allele carriers did not show a different median survival time, even when the analysis was stratified by cancer histotype.
Conclusions: Our study reports for the first time a protective effect of the ε2 allele against GC, probably due to its better antioxidant properties if compared with the ε3 or ε4 alleles. According to our results, Apolipoprotein E may play a different role in carcinogenesis other than its well-known role in regulating blood serum cholesterol levels.

6509 POSTER

Atrophy, Intestinal Metaplasy and Dysplasia in the Operation Material of Gastric Cancer

I. Liepniece-Karele[1], D. Janciauskas[2], S. Jaudzema[2], A. Sivins[2], G. Ancans[2], M. Leja[2]. [1]*Riga Eastern Clinical University Hospital, Department of Pathology, Riga, Latvia;* [2]*University of Latvia, Department of Medicine, Riga, Latvia*

Background: Typically gastric cancer is a result of Helicobacter pylori associated chronic gastritis. The aim of our study was to evaluate intestinal metaplasia, atrophy and dysplasia in the operation material of gastric carcinoma.
Materials and Methods: The retrospective analysis of 331 patients with gastric carcinoma treated in Latvia Oncology Centre during 2000–2005 has been done. We evaluated either presence or absence of dysplasia in the operation material as well as the grade of intestinal metaplasia [enteric (GI), enterocolic (GII), colonic (GIII)]. The atrophy was analyzed in the antral part and in the corpus. For statistical analysis the SPSS statistical software version 12 was used.
Results. In most cases (29.8%) carcinoma was localised in the lower third part of stomach. According to the WHO classification adenocarcinoma was in 92% cases. The tubular subtype of adenocarcinoma were in 58.4% cases (59.6% of them were poorly differentiated). Lauren type was diffuse in 44.1% cases, 34% intestinal. Mostly (34%) tumours were T2 stage (the invasion in muscularis propria).

Table 1. Analysis of cancer precursor lesions in the gastric corpus and antral part.

Value	Percent	Chi-square test (asymp.sig. [2-tailed])
Intestinal metaplasia in corpus	15	
Intestinal metaplasia in antrum	41.5	0.000
Atrophy in corpus	14.8	
Atrophy in antrum	43.7	0.000
Dysplasia in corpus	5.3	
Dysplasia in antrum	28.6	0.000

The atrophy in antral part in Lauren intestinal type carcinoma were in 80 cases but diffuse type in 46 cases (p = 0.000). We detected atrophic changes in the corpus in 22 cases of intestinal and diffuse carcinoma in 17 cases (p = 0.227).
Dysplasia in antral part of intestinal type of carcinoma were in 70 cases, but in diffuse type − in 15 cases (p = 0.000). But the presence of dysplasia in 50.8% cases in the corpus and in 4.2% cases in the antral part was difficult to analyse.
Conclusions:
1. More frequently we detected precancerous lesions in antral part of stomach.
2. Mostly the atrophy and dysplasia were associated with Lauren intestinal type of carcinoma.

6510 POSTER

SIRT6 Induces IL-8 and TNF-a Expression in Pancreatic Cancer Cells

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Background: SIRT6 is a NAD^+-dependent lysine-deacetylase that plays a role in aging, metabolism, stress resistance and genomic stability. Recently, SIRT6 was found to regulate the expression of cytokines such as TNF-α and IFN-γ at a post-transcriptional level in immune cells. Inflammatory cytokines have been reported to be expressed in pancreatic cancer and may be involved in the promotion of angiogenesis, invasion and metastasis.
Material and Methods: We used the pBABE-puro retroviral vector system to stably over-express wild type (WT) SIRT6 and the catalytically inactive mutant SIRT6 H133Y in the human pancreatic cancer cell line BxPC-3. Moreover SIRT6 was silenced using the retroviral pRETROSUPER RNA interference (RNAi) system. To induce cytokine expression, cells were stimulated for 48 h with phorbol 12-myristate 13-acetate (PMA), an activator of protein kinase C (PKC) and inducer of invasion. Alternatively, we treated BxPC-3 cells with the nicotinamide phosphoribosyltransferase (Nampt) inhibitor FK866 to reduce intracellular NAD^+ levels or with the sirtuin inhibitors nicotinamide and sirtinol, and stimulated them for 48 h with PMA. The expression of IL-8 and TNF-α was determined by quantitative real-time PCR and secreted cytokines were assessed by ELISA.
Results: Quantitative PCR and ELISA experiments revealed that IL-8 and TNF-α expression was induced significantly in BxPC-3 cells over-expressing SIRT6 WT as compared to vector bearing cells, while in cells over-expressing the inactive SIRT6 H133Y cytokine levels were unaltered. In cells where SIRT6 expression was knocked-down by RNAi, IL-8 and TNF-α expression was downregulated at the mRNA level. Both the reduction of intracellular NAD^+ levels and the inhibition of SIRT6 by nicotinamide or sirtinol led to reduced IL-8 and TNF-α expression in BxPC-3 cells.
Conclusion: Our results show that SIRT6 promotes IL-8 and TNF-α expression in pancreatic cancer cells. This suggests that SIRT6 could serve as a novel therapeutic target in cancers producing these pro-inflammatory, chemotactic, and pro-angiogenic cytokines.

6511 POSTER

Restoration of Activity in Mannose-binding Lectin Complement Pathway in Patients With Advanced Pancreatic Cancer Treated With Intravenous Omega-3 Rich Lipid Infusion and Gemcitabine is Associated With Improved Outcome

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Background: The immunomodulatory actions of omega-3 fatty acid (n-3FA) rich lipid infusions as part of parenteral nutrition are well recognised. In animal models of pancreatic cancer, n-3FA have shown anti-neoplastic activity, although the mechanisms of this are unclear. There is evidence to suggest complement may play a role in the host response to cancer, although the precise interactions and their relative importance of different complement pathways in pancreatic cancer are unknown.
Materials and Methods: As part of a phase II single-arm trial investigating gemcitabine plus intravenous n-3FA rich lipid emulsion (Lipidem, BBraun, Melsungen) in patients with locally advanced or metastatic pancreatic cancer, serum samples were taken prior to treatment, and then weekly thereafter for 8 weeks. Classical (CP), alternative (AP) and mannose-binding lectin (MBL) pathway activity was assessed using an enzyme immunoassay kit. Results were correlated with time to progression as determined by modified RECIST criteria on CT scan. The trial was registered with clinicaltrials.gov: NCT01019382 and sponsored by University Hospitals of Leicester.
Results: 20 patients were assessable for progression on CT of which all had normal baseline activity in CP and AP pathways. 8/20 (40%) had evidence of reduced function of MBL pathway at baseline with activity <70%. 5/8 (63%) had restoration of MBL function to >70% during treatment associated with a significantly prolonged time to progression (TTP) over non-restored patients (median TTP 5.6 vs 1.5 months p = 0.04). There was no difference in TTP between normal and reduced MBL function at baseline 5.3 vs 5.3 months (p = 0.67).
Conclusions: Gemcitabine plus n-3FA rich lipid emulsion may restore complement activity, which may contribute to improved outcome. A double-blind randomised controlled trial is planned to assess the independent contribution of n-3FA. Further studies to elucidate the potential mechanisms for complement interaction are required.

6512 POSTER

Stromal Cell-derived Factor-1 Alpha is a Novel Independent Poor Prognostic Factor in Gallbladder Carcinoma

H.J. Lee[1], Y.S. Oh[1], Z.L. Liang[2], H.Y. Kim[1], H.J. Yun[1], S. Kim[1], D.Y. Jo[1], J.K. Min[3], J.M. Kim[2]. [1]*Chungnam National University Hospital, Internal Medicine Cancer Research Institute, Daejeon, Korea;* [2]*Chungnam National University Hospital, Pathology, Daejeon, Korea;* [3]*Korea Research Institute of Bioscience and Biotechnology, Therapeutic Antibody Research Center, Daejeon, Korea*

Background: Although recent studies have suggested an importance of the stromal cell-derived factor-1α (SDF-1α) in the progression of