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

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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

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

various malignancies, its role in gallbladder carcinoma (GBC) remains undiscovered.
Methods: We studied SDF-1α protein expression in 72 specimens of GBC using immunohistochemistry, and analyzed the clinicopathological features and clinical outcomes. GBC cell lines, SNU-308 and JCRB1033, were studied *in vitro* and *in vivo*. Specific depletion or overexpression of CXCR4, which is a receptor for SDF-1α, in GBC cell lines was achieved by expression of a small interfering RNA (siRNA) against CXCR4 and lentivirus-mediated transduction, respectively.
Results: We observed the constitutive expression of SDF-1α in patients with gallbladder carcinoma (GBC) and recognized inverse correlation between the level of SDF-1α expression and their overall survival. In addition, SDF-1α expression was significantly associated with high histologic grade and lymph node involvement. Multivariate analyses showed that SDF-1α expression (HR, 8.252; 95% CI, 1.116–61.043; $P = 0.039$) and lymphatic invasion (HR, 10.346; 95% CI, 1.304–82.080; $P = 0.027$) were independent risk factors for overall survival. Furthermore, we demonstrated functional involvement of SDF-1α and its receptor CXCR4 in the growth, motility, invasiveness, and adhesiveness of GBC cells. Stable depletion of CXCR4 even with SDF-1α stimulation led to a significant decrease in GBC cell proliferation, migration, and invasion while overexpression of CXCR4 with SDF-1α stimulation showed enhanced these cellular activities and increased intracellular signaling through ERK, AKT and FAK. In a GBC xenograft nude mouse model, SDF-1α overexpression stimulated tumorigenicity of GBC cells.
Conclusions: These results indicate that GBC cells express both SDF-1α and its receptor by tumour itself and SDF-1α may have a role in GBC progression through an autocrine mechanism. Thus, targeting SDF-1α and its receptors may provide a novel therapeutic strategy for GBC treatment.

6513 POSTER

Reporting Patient Characteristics and Stratification Factors in Randomized Trials of Systemic Chemotherapy for Advanced Gastric Cancer

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Background: There is no consensus on what patient characteristics are most suitable to report or be used as stratification factors in clinical trials for advanced gastric cancer (AGC), to our knowledge.
Patients and Methods: We conducted a comprehensive review of published randomized trials for AGC to examine the patient characteristics that were reported.
Results: Among the 67 analyzed trials, age, gender, performance status, proportion of measurable disease, and previous gastrectomy were frequently reported (>69%). Histology, number of disease sites, and adjuvant treatment were reported in less than 50% of trials. Although the reporting of second-line chemotherapy has increased in recent trials, it remains at less than 50%. Notably, recent trials have tended to include patients with better performance status and less locally advanced disease, with Asian trials more frequently including patients with more diffuse histology and less locally advanced disease or liver metastasis than non-Asian trials. Stratification was conducted in approximately 60% of trials using quite variable stratifying factors.
Conclusion: Inconsistency exists in the reporting of patient characteristics, the characteristics themselves, and use of stratification factors in clinical trials for AGC. A consensus set of important patient characteristics and strata may be necessary to conduct and interpret quality, randomized studies.

6514 POSTER

Genetic Polymorphism of IGF1 Predicts Recurrence in Patients With Gastric Cancer Who Have Undergone Curative Gastrectomy

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Background: To our knowledge, no reports have evaluated the effects of genetic polymorphisms of IGF1 on clinical outcomes of gastric cancer patients.
Methods: We retrospectively analyzed the impact of IGF1 polymorphisms on recurrence-free survival (RFS) in 430 patients with gastric cancer who underwent curative gastrectomy between 2001 and 2005 in our institution.
Results: Among the 430 gastric cancer patients, 345 were pathological stage I or II, while 85 were stage III or IV. The median 5-year RFS rate was 85.3% (95% confidence interval, 81.4–88.5). In a multivariate Cox model (adjusted for age, gender, histology, pathological stage, adjuvant chemotherapy, and history of diabetes), two IGF1 polymorphisms, rs1520220 and rs2195239, were significantly associated with RFS (HR 0.60, 95% CI, 0.40–0.91; and HR 0.60, 95% CI, 0.41–0.89, respectively, in a per-allele model). When stratified by stage (I-II vs. III-IV), rs1520220 in particular was associated with RFS in patients with stage III-IV disease, with a P value for interaction of 0.01.
Conclusion: Our findings indicate that genetic polymorphisms of IGF1 may have a substantial effect on recurrence for gastric cancer patients who have undergone curative gastrectomy. This information may help identify population subgroups that could benefit from IGF-1 targeting agents.

6515 POSTER

Application of the Trifunctional Antibody Catumaxomab as Part of a Multimodal Approach in Resectable Gastric Cancer is Feasible and Promotes the Development of Tumour-specific Immune Responses

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Background: Although perioperative chemotherapy (CT) is beneficial in gastric cancer (GC), a significant number of patients will eventually relapse. The trifunctional antibody (Ab) catumaxomab targets (1) the epithelial cell adhesion molecule (EpCAM) on malignant cells, (2) CD3 on T cells, and (3) triggers Ag-presenting cells via their Fcγ-receptor. While catumaxomab has been approved for the treatment of malignant ascites, it has not been investigated in a perioperative setting and the immune mechanisms behind its clinical effects have not conclusively been elucidated.
Methods: In a phase II study, patients with operable GC received neoadjuvant platinum-based CT followed by 10 μg of catumaxomab intraoperatively and 4 consecutive doses (10–20–50–150 μg) applied intraperitoneally in the adjuvant setting. Primary safety endpoint was the rate of predefined postoperative complications. Efficacy endpoints included disease-free (DFS) and overall survival. The immunomodulatory effect of catumaxomab was investigated before surgery, after application of the first dose, and 1 month post treatment.
Results: 54 patients completed ⩾1 cycle of CT, surgery and ⩾1 catumaxomab dose. Most of these patients (N = 30; 56%) received all five catumaxomab infusions. The primary endpoint was met as predefined postoperative complications were reported for only 18 patients (33%; 95% CI: 21−48%) which was below the predefined maximum tolerable rate of 62%. Most frequent complications were pulmonary infection, anastomosis insufficiency and abscess. Immunomonitoring of 6 selected patients revealed a transient decrease in peripheral CD4+ T cells with an effector and T-helper (Th)-1 phenotype directly after Ab application. All patients investigated evidenced pre-existing EpCAM-specific CD4+ and/or CD8+ T cells. While these T cells disappeared from the peripheral blood (PB) immediately after Ab exposure, we detected increased numbers of peripheral EpCAM-specific cells 4 weeks after catumaxomab treatment. During a 1-year follow-up, 13/49 evaluable pts (27%) relapsed, 2 of whom died. DFS was 74% (95% CI: 61−86%).
Conclusions: Catumaxomab as part of a multimodal therapy is a feasible option for primarily resectable GC. The 1-year follow-up efficacy data suggest a beneficial effect on DFS. Catumaxomab might exert its clinical effects i.e. by causing a redistribution of effector and Th1-type cells from the PB into peripheral tissues and expanding pre-existing EpCAM-specific T cells.

6516 POSTER

Management of Stage 4 Metastatic Neuroendocrine Disease − Outcomes and Cost-effectiveness

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Background: Management of hepatic neuroendocrine metastases remains controversial. Surgery with curative intent aims to resect all pre-operatively identifiable disease, whilst cytoreductive surgery for symptom control is appropriate when 90% of tumour burden can be removed. Radiological and symptomatic recurrence rates remain high. This study aimed to