to be an acceptable alternative to infusional 5-FU/LV in combination therapy. Updated results including data on second-line treatment will be presented at the meeting.

296 POSTER

Microarray expression analysis indicates a central role for matrix-metalloproteinases MMP-1, MMP-3, MMP-9 and TIMP-3 in the metastatic process of colorectal carcinomas

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Background/Aims: To date, the molecular basis of the metastatic process is understood only by part. However, the family of matrix-metalloproteinases seems to be involved due to their ability to degrade the extracellular matrix, to induce angiogenesis and to influence apoptosis. In this study the gene expression profile of colorectal carcinomas and their corresponding liver metastases were analysed using gene-expression microarrays to get a deeper view of the genes and pathways involved in metastasis.

Material/Methods: After written informed consent tumour material from nine colorectal primaries and biopsies from the corresponding liver metastases were taken intraoperatively and immediately snap-frozen in liquid nitrogen. The tissues were laser-microdissected, amplified and hybridised to Affymetrix U-133A microarrays according to the manufacturers instructions. 18 gene expression datasets comprising 22,283 human genes and ESTs each were analysed for statistic significance between colorectal carcinomas and liver metastases Results were verified by RT-PCR.

Results: The gene-expression for MMP-1, MMP-3, MMP-9 and TIMP-3 was statistically significant increased in colorectal carcinomas in contrast to liver metastases. Additionally changes in gene expression could be detected for collagens I, III, V, X, laminin, heparansulfate, transmembrane-4 family members and tetraspan. Furthermore, expression changes were obvious for genes involved in angiogenesis, e.g. the endothelin receptor or the plasminogen activator. The increased expression of MMP regulatory genes (CDC42, RAS and FOS) confirm the hypothesis for the involvement by this pathway.

Conclusions: Using genome-wide gene expression analysis we could show a central role for MMP-1, MMP-3, MMP-9 and TIMP-3 in the metastatic process in vivo. Further potential candidates with significant expression differences between primary and metastatic tumours are profen for relevance at present.

297 POSTER

Preliminary phase I results of the oral, once-daily angiogenesis inhibitor PTK787/ZK 222584 (PTK/ZK) in combination with chemotherapy for the treatment of metastatic colorectal cancer

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Background: PTK/ZK is a novel, oral angiogenesis inhibitor that potently inhibits the vascular endothelial growth factor receptor-1 and -2 tyrosine kinases, important receptors contributing to new blood vessel formation during tumor growth and metastasis. Daily administration of PTK/ZK, alone and in combination with chemotherapy, has been generally well tolerated in more than 450 patients, and PTK/ZK significantly reduced tumor blood supply with associated significant reductions in the size of colorectal cancer liver metastases.

Material and Methods: This study assessed safety and preliminary efficacy of PTK/ZK in combination with 2 different chemotherapy regimens. Previously untreated patients with measurable, advanced-stage colorectal cancer were treated with oral PTK/ZK plus either oxaliplatin/5-fluorouracil (5-FU)/leucovorin (FOLFOX4) or irinotecan/5-FU/leucovorin (FOLFIRI) in a phase I/II, dose-escalation study. PTK/ZK was administered at doses ranging from 500 to 2,000 mg/day. Oxaliplatin (85 mg/m^2) or irinotecan (180 mg/m^2) was administered on day 1, and leucovorin (200 mg/m^2 via 2-hour infusion) and 5-FU (400 mg/m^2 bolus followed by 600 mg/m^2 via 22-hour infusion) were administered on days 1 and 2 every 2 weeks. Tumor response was assessed every 12 weeks.

Results: To date, 35 patients have been treated with PTK/ZK plus FOLFOX4, and 16 patients have received PTK/ZK plus FOLFIRI. Both combinations were generally well tolerated. In the FOLFOX4 arm, lightheadedness and dizziness were dose limiting at 2,000 mg/day PTK/ZK; the maximum tolerated dose has not yet been reached in the FOLFIRI arm (with dosing currently at 1,250 mg). Preliminary results suggest that PTK/ZK did not affect the safety profile of either chemotherapy regimen or alter the pharmacokinetics of oxaliplatin. Among 21 evaluable patients treated with PTK/ZK + FOLFOX4, 9 (43%) had a partial response (PR), 8 (38%) had stable disease, and 4 (19%) had progressive disease. For 29 patients to date, median time to progression is 10.8 months (95% CI, 6.9-13.4 months). Among 9 evaluable patients treated with PTK/ZK + FOLFIRI, 4 (44%) had a PR and 5 (56%) had stable disease.

Conclusions: These preliminary results suggest that PTK/ZK combined with FOLFOX4 and FOLFIRI is feasible and well tolerated. The results are promising, particularly with regard to time to progression, and patients continue to be accrued to this trial.

298 POSTER

Comparison between radiotherapy and neoadjuvant chemotherapy and radiotherapy in a population based series of epidermoid anal carcinomas

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Background: Primary treatment of epidermoid anal cancer is radiotherapy (RT) alone, or in combination with chemotherapy. Radical surgery is reserved for poor responders or recurrences. The use of concomitant chemoradiotherapy as well as neoadjuvant chemotherapy followed by RT has been reported in the literature. This study presents results from a large population-based material and provides comparison between different treatments.

Material and methods: Between 1985 and 2000, 308 patients with invasive epidermoid anal cancer were diagnosed in the Stockholm Health Care Region. All patients were prospectively recorded. Treatment was given according to defined protocols. Between 1985 and 1991 RT+/-concomitant bleomycin was used for all tumours. Between 1989 and 2000 patients with locally advanced tumours (T>4 cm or N+) received neoadjuvant platinum based chemotherapy followed by RT, whereas smaller lesions were treated with RT alone.

Results: Among the 276 patients (90%) who were treated with curative intent, 264 (96%) received treatment in accordance with the protocols. Among 142 patients with locally advanced tumours treated with either RT+/-concomitant bleomycin (n=51) or neoadjuvant platinum based chemotherapy and RT (n=91), the complete response rate (CR) was 87%. Patients receiving neoadjuvant chemotherapy had a significantly higher CR-rate compared to those treated with RT+/-bleomycin (92 vs. 76%, p<0.01). The overall 5-year survival rate among patients with locally advanced tumours was 59%. A significantly higher 5-year survival rate was found in the neoadjuvant group (63 vs. 44%, p<0.05). Isolated locoregional failures, either as residual tumour after completion of therapy or as recurrences, occurred significantly more frequent among patients receiving RT+/-bleomycin (31 vs. 14%, p<0.05). Multivariate analyses revealed treatment as an independent prognostic factor.

Conclusions: The results suggest that neoadjuvant platinum based chemotherapy and RT is superior to RT alone or with bleomycin in the treatment of locally advanced cases of epidermoid anal cancer. For confirmation of superiority to the present reference regimen, being RT with concomitant 5-FU and mitomycin C (or cisplatinum), a randomised trial is needed.

299 POSTER

Screening for single nucleotide polymorphism (snp) in association with sporadic colorectal cancer.

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Background: The cumulative life time risk of developing sporadic colorectal cancer (CRC) in the Western Europe is approximately 6%. A first-degree relative to patients with sporadic CRC is twice as likely to develop the disease. We believe that single nucleotide polymorphism (SNP) may be important for susceptibility for disease development. However screening of

a large number of SNP's based on analysis of individual samples is time consuming and expensive.

Materials and methods: We have established a pooling strategy for detection of SNP's in genes, which are known in the pathogenesis of colorectal cancer, including APC, beta-catenin, E-cadherin, K-ras, p53 and others. The SNP's are selected from the dbSNP-NCBI database (). We have constructed pools of DNA from 230 patients with diagnosed sporadic colorectal cancer and from 540 controls. 100 ng. of genomic DNA from each individual is used for the pool. The pool holds DNA for approximately 1500-2000 individual SNP analysis.

The method involves PCR amplification of genomic DNA fragment including the SNP, single base extension (SBE) reaction of SNP using fluorescent-labelled ddNTP followed by capillary electrophoresis of single base reaction products.

We aim at screening 500 SNP's for association with disease development covering approximately 50 genes.

Results: SNP's are screened by analyzing frequency in case-pool and in control-pool. SNP's showing a minor allele frequency of >10% are further analyzed, and candidates showing difference in allele frequency between the two pools are further validated by sequencing.

Preliminary results screening 63 SNP's in 7 genes show:

Positive PCR product Positive SBE product Minor allel frequency >10% Non conclusive data

60/63 = 95% 59/61 = 97% 25/61 = 41% 2/61 = 3%

The total number of single reactions for screening of the 63 SNP's in pools is 704 as compared to 48.510 reactions by analyzing individual samples, thereby reducing the number of analysis by a factor of 69.

Conclusions: We have established a method for screening of large number of SNP's in genes suspected for a potential role in development of sporadic colorectal cancer. The method significantly reduces the total number of reactions and the amount of DNA used for SNP analysis, as compared to analysis of individual samples, and identifies SNP's suspected for association with disease development.

300 POSTER

Effects of capecitabine (Xeloda) on quality of life (QoL) in patients with metastatic colorectal cancer (MCRC)

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Background: While outcomes such as objective response, time to disease progression and overall survival are well-established measures of treatment response, the QoL benefits of oral treatments, such as the novel fluoropyrimidine capecitabine (Xeloda®), are important when choosing appropriate therapy for MCRC.

Patients and Methods: QoL was assessed in a sample of 209 patients receiving oral capecitabine as second- or third-line therapy for MCRC. Patients completed the EORTC QLQ C-30 questionnaire and the specific model for colorectal cancer (CR-38) at baseline, before the first cycle of treatment, at weeks 7 and 13, and at the end of treatment. Linear models with repeated measures of the scores were used to analyse questionnaire responses over time. The proportion of patients with an improvement, stabilisation or worsening of QoL scores from week 7 onwards was analysed with generalised linear models for repeated measures, using the generalised estimating questions technique. Statistical analysis was performed using an SAS programme (system version 8.2).

Results: Patient characteristics were as follows: male/female, 54.5%/45.5%; mean age 53.9 years (range 25.0-72.0 years); white/Caucasian, 89%. Almost 50% of patients completed the questionnaires at all time points. Variables for which a statistically significant improvement in QoL over time was detected included global health status (p=0.04), physical functioning (p=0.04), financial problems (p=0.008), future perspective (p=0.006) and weight loss (p=0.0008). The proportion of patients that remained stable or improved was * 70% for most scales. At least 30% of patients reported improvements in the following QoL scales from week 7 onwards: global health status (38%); social functioning (36%); fatigue (36%); pain (35%); micturition problems (33%); role functioning (31%); emotional functioning (31%); future perspective (31%); chemotherapy side-effects (31%). After all time points *"at the end of treatment?"*, 46% of patients showed an improvement in global health status and 24% had stable scores. In addition, 45% of the total number of patients experienced improvement in fatigue and 43% had improvement in social functioning.

Conclusion: These findings indicate that the efficacy, safety and convenience of capecitabine allow patients to maintain a normal lifestyle and have a direct impact on QoL. This important measure should be considered along with established treatment outcomes when deciding on patient therapy in MCRC.

301 POSTER

Peritoneal carcinomatosis of colorectal origin: results of palliative surgery and systemic chemotherapy.

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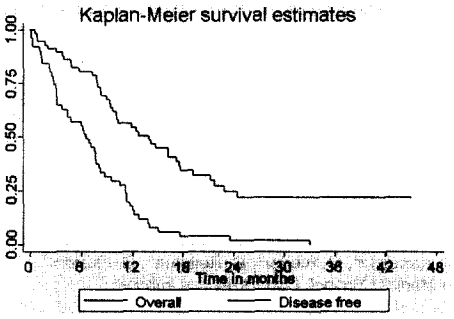
Back ground: Peritoneal carcinomatosis (PC) has a grave prognosis. New treatments like extensive surgical resection and intra-peritoneal chemotherapy may enhance survival. This novel treatment seems to create an improved survival in patients with PC of CRC origin without distant metastasis. Very little is known about the results of systemic chemotherapy in these patients.

Methods: 57 patients with proven peritoneal carcinomatosis of colorectal origin without distant metastasis treated with palliative surgery and fluorouracil (5FU)(400mg/m^2) and folinic acid (80mg/m^2) once weekly, or irinotecan (CPT 11) (350mg/m^2) every three weeks in patients treated with 5FU within 12 months prior to study entry were studied. The median follow-up was 40 months (range 2.5 - 62 months). The following prognostic factors were analysed: gender, location of primary CRC, PC at diagnosis CRC or recurrent CRC and palliative resections. Analysis: Survival and progression free survival was calculated by the Kaplan Meyer method. Prognostic factors where analysed using the log-rank test.

Results: The median survival of peritoneal carcinomatosis was 14.1 months when treated by palliative surgery and systemic chemotherapy. Median progression free survival was 7.7 months. Kaplan Meyer curves are shown in the figure Female gender correlate with improved survival, but this did not reach significance (p=0.0741). Patients in whom a resection was possible had a significant better prognosis (improvement from 8.3 to 17.3 months (p=0.0042)). None of the other factors were related to survival.



Conclusion: Survival of PC of CRC origin is poor when treated by palliative surgery and systemic chemotherapy only. If a palliative resection is possible the survival significantly improves probably related.

302 POSTER

Equal prognosis of elderly and non-elderly patients with metastatic colorectal cancer and 5-FU treatment: a retrospective analysis.

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Introduction: There is, uncertainty as to what extent systemic adjuvant or palliative chemotherapy should be offered to elderly patients with colorectal cancer. This fact is related to the unfortunate underrepresentation or even