AUC/CPT11 in both arms. $Cl_{tot}$ (17.6 vs 17.5 l/H) and Vss (150 vs 151) of CPT 11 were identical in both arms. Cmax and AUC of SN 38 gluc and APC were slightly lowered under C-MAB due interpatient variation. Side effects of C-MAB 500 mg/m$^2$ every 2 weeks were comparable to those reported for standard dose, toxicity of concomitant CPT 11 was not increased.
**Conclusion:** This PK trial confirms safety and non influence of a biweekly instead of standard weekly C-MAB on the PK profile of CPT11 and SN 38 and supports its clinical use as a simplified scheduling in combination with FOLFIRI biweekly application.

| n = 11 | CPT 11 | | | | Cetuximab + CPT 11 | | | |
|---|---|---|---|---|---|---|---|---|
| mean (+SE) | CPT11 | SN38 | SN38gluc | APC | CPT11 | SN38 | SN38gluc | APC |
| cmax ng/ml | 3828 (569) | 40.7 | 153 (50) | 266 (133) | 3633 (474) | 37.3 | 109 (30) | 179 (126) |
| AUC inf ng/ml.H | 21147 (5395) | 519 (261) | 3330 (2441) | 4623 (4100) | 20701 (4042) | 533 (186) | 2674 (1478) | 3095 (3000) |

**6091** POSTER

**Associations of various gene polymorphisms with toxicity in colorectal cancer patients receiving oral uracil and tegafur plus leucovorin: a prospective study**

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**Background:** To assess the predictive value of polymorphisms within nine genes, which relates to 5-FU metabolism, for toxicity in patients treated with oral uracil/tegafur (UFT) plus leucovorin (LV) in a prospective study.
**Material and Methods:** Ninety-nine patients with stage II and III carcinoma of the colorectum were treated with oral UFT+LV. The study cohort consisted of 58 men and 41 women, with a mean age of 65 years ranging from 30 to 80 years. The performance status was 0 and 1 in 72 and 27 patients, respectively. The primary tumor was located in the colon in 59 cases and in the rectum in 40 cases. The depth of invasion according to the tumor-node-metastasis classification was 7 $T_1$ or $T_2$ tumors, 84 $T_3$ tumors, and 8 $T_4$ tumors. There were 51 stage II and 48 stage III tumors. Germ line DNA from patients was obtained and genotyped for TS VNTR, TS VNTR+G/C SNP, and TS 1494del6, and DPD IVS14+1G>A, T85C, A1627G, and G2194A, and OPRT G638C, and MTHFR C677T, and A1298C, and MTR A2756G, and MTRR A66G, and SLC19A1 G80A, and CYP2A6 variant (*4, *7, *9 and *11), and UGT1A1 –insTA(*28), G211A(*6), C1813T, and T3279G(*60) using PCRs and RFLP. Toxicity was graded by National Cancer Institute Common Toxicity Criteria version 2.0.
**Results:** The 99 patients had received a total of 444 treatment courses (median, 5 courses; range 0.1 to 5 courses). The most common type of toxicity was fatigue. However, the incidence of grade 3 or 4 fatigue was very low. 13 patients had grade 2 or 3 hyperbilirubinemia. Six patients each had grade 3 diarrhea or anorexia. Allele frequencies of all 5-FU related genes were successfully assessed for all 99 patients. The distribution is in close agreement with that predicted by Hardy-Weinberg equilibrium. OPRT polymorphism was associated with severe overall toxicity, especially grade 3 diarrhea in univariate analysis (P = 0.007, P = 0.031, respectively). The multivariate logistic regression models revealed that only OPRT polymorphism had an independent value to predict grade 3 overall toxicity (odds ratio, 25.80 for patients with the G638C homozygous type compared with patients with heterozygous or wild type, P = 0.004) and grade 3 diarrhea (odds ratio, 23.25, P = 0.013). Polymorphisms in DPD A1627G or MTHFR C677T were associated with moderate to severe toxicity (P = 0.048, P = 0.021, respectively). Polymorphisms of UGT1A1 G211A or T3279G were also associated with hyperbilirubinemia (P = 0.010, P = 0.018, respectively).
**Conclusions:** OPRT polymorphism seems to be a useful marker for predicting severe toxicity to oral UFT+LV therapy.

**6092** POSTER

**Serum microRNAs as potential biomarkers for colorectal cancer**

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**Background:** Colorectal cancer (CRC) is a common and fatal disease, with a strong correlation between stage and prognosis. Current screening methods for CRC have significant limitations and newer technological approaches are eagerly searched for. Circulating nucleic acids in body fluids offer unique opportunities for early diagnosis of various clinical conditions. Here we propose microRNAs, a family of small non-coding regulatory RNAs involved in human development and pathology, as an emerging class of effective serum biomarkers for CRC.
**Methods:** Rosetta Genomics has developed protocols for extracting and quantifying microRNA levels in serum and other body fluids. Serum levels of 364 microRNAs were measured using qRT-PCR in a semi-high-throughput manner on sera from 10 healthy controls and 10 CRC patients (Pts). A subset of the identified microRNAs, demonstrating significant differences in abundance between the two groups, was studied on a larger cohort of 118 pts and controls.
**Results:** By semi-high-throughput profiling of microRNAs in a small set of serum samples from CRC pts and healthy controls, we identified a subset of microRNAs that show significant differential abundance between the two groups. Measuring the levels of 22 microRNAs on a cohort of 118 pts and controls, we show that serum levels of microRNAs can be very informative in the identification of CRC.
**Conclusions:** Our results demonstrate that we have developed highly sensitive methods that enable the extraction and measurement of cell-free microRNAs in body fluids. Here, we demonstrate that certain microRNAs are found in different amounts in sera of CRC pts compared with healthy controls. Thus, circulating microRNAs represent promising candidates for robust, sensitive and easily accessible biomarkers in CRC.

**6093** POSTER

**A significance of circulating endothelial progenitor cells in metronomic chemotherapy using CPT-11 and bevacizumab for colon carcinoma**

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**Background:** Conventional cytotoxic anticancer drugs have anti-angiogenic effects, which could contribute to their efficacy, however, conventional chemotherapy requires 2- to 3-week break between successive cycles because of toxicity by MTD administration. The anti-angiogenic effects of chemotherapy seemed to be optimized by administering such drugs 'metronomically' – in other words in small dosages on a frequent schedule (daily, several times a week, or weekly) in an uninterrupted manner. It has been shown that the efficacy of metronomic chemotherapy can be significantly increased when administered in combination with anti-angiogenic drugs, such as antibodies against vascular endothelial growth factor (VEGF) or VEGF receptor 2, and some metronomic chemotherapy regimens induce sustained suppression in circulating endothelial progenitor cells (CEP). We have investigated antitumor efficacy of metronomic chemotherapy using CPT-11 combined with or without bevacizumab in colon cancer. We have also evaluated the relationship between the antitumor activity and circulating endothelial cell (CEC) and CEP.
**Materials and Methods:** A total of $10^6$ KM12SM colon cancer cells/0.2 ml PBS was implanted into the subcutis of BALB/c nude mouse. The mice were divided into 4 groups according to treatment. The Group A received i.p. injection of 40 mg/kg CPT-11 every two weeks (MTD), the Group B received i.p. injection of 10 mg/kg CPT-11 twice per week (metronomic), the Group C received i.p. injection of 10 mg/kg CPT-11 twice per week combining with i.p. injection of 5 mg/kg bevacizumab twice per week. The Control Group received i.p. injection of 0.2 ml PBS every week. CEC and CEP in peripheral blood were evaluated by flow cytometry and microvessel density (MVD) was evaluated using immunohistochemical staining for CD34 in tumor tissues.
**Results:** The antitumor activity in the Group B (metronomic chemotherapy) was significantly higher than that in Group A. The antitumor activity in the Group C was significantly higher than that in Group B. A significant inhibition on CEP in day 15 was found compared with that in the Control Group, while there was no significant difference in CEC and CEP between each group in day 8. The MVD at day 15 in the metronomic groups was significantly lower than that in the conventional group.
**Conclusion:** The metronomic chemotherapy of CPT-11 with or without bevacizumab for colon cancer was more effective than the MTD therapy via antiangiogenic effects. Measurement of CEP may be a predictive factor for metoronomic chemotherapy in colon cancer.