726 POSTER

PROGRESSION OF FAP-DERIVED HUMAN COLONIC CELLS AFTER TRANSFER OF THE SRC ONCOGENE ALONE OR COMBINED WITH THE POLYOMA EARLY REGION. INTERACTION WITH THE MET/HGF SYSTEM

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Functional insertion of activated src or PyMT oncogenes induced the tumorigenic potential of PC AA/C1 cells in athymic mice. Transfer of the Py early region genes alone or combined with c-src shortened the latency period and induced highly progressive tumors. PC cells transfected by mutated src induced exhibited elevated $pp60^{src}$ tyrosine kinase activity, HGF-dependent invasion in collagen gels and overexpression of MET by Northern and Western blots. Expression of the HGF gene was detected by RT-PCR and Southern blot in parental and oncogene-transfected cells.

Our results indicate that activation of the src tyrosine kinase, an early event during human colon cancer progression, may be involved: (1) in the adenoma-carcinoma conversion, (2) activation of the invasion and metastatic cascades under the control of HGF and MET.

727 POSTER

A PHASE II STUDY OF CPT 11 (IRINOTECAN) IN REFRACTORY TO 5 FU COLORECTAL CANCER (CRC) WITH, PREVENTIVE TREATMENT OF DELAYED DIARRHEA BY ACETORPHAN

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According to Phase I data, Acetorphan a new anti-secretory anti-diarrheal agent might reduce the incidence and severity of CPT 11 induced diarrhea. In an attempt to confirm these results, an open randomized study has been performed, using this specific enkephalinase-inhibitor: Acetorphan (A). All patients (pts) had advanced CRC refractory to 5 FU and were treated with CPT 11 at the dose of 350 mg/m^2 every 3 weeks.

In this study, the role of prophylactic A, 100 mg × 3/d has been randomly assessed versus no prophylaxis. Eighty eight pts have been so far entered and 45 are evaluable. Preliminary results suggest no difference in term of incidence or severity of D, but a trend towards a shorter duration and later occurrence of D in cycle 1 (3 versus 4.5 days and day 6 versus day 5 respectively) in patients receiving A and surprisingly a decrease in the incidence of grade 3 + 4 (OMS) neutropenia and febrile neutropenia.

Conclusion. The new anti-diarrheal agent A, may be of interest in the prophylactically management of CPT 11 induced diarrhea. Final results of these studies will be presented.

728 POSTER

EXPRESSION OF ADHESION MOLECULES RELATED TO TUMOUR-PROGRESSION IN COLORECTAL CARCINOMA: GRADING, STAGING AND FOLLOW UP

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Introduction: Tumour progression and metastasis is accompanied by altered expression of adhesion molecules. The purpose of this prospective study was to analyse expression of adhesion molecules in colorectal carcinomas based on a cohort derived from a single surgical oncology center. At that end CD44 variant isoforms, E-Cadherin, β-Catenin as well as α- and β-integrin subunits were investigated both on the mRNA- and on the protein level. Snap frozen samples of normal colorectal mucosa, primary tumours, and metastases were collected from 120 patients during 1992–1994. All data were correlated to TNM-stages and clinical status. *Results:* CD44H is broadly expressed in all tissues. CD44 variant isoform expression is transient, being up-regulated as early as in adenomas. Maximum expression is observed in UICC stage III primary tumours, but significant loss of CD44 isoform expression is observed in all sites of metastasis. Adherent junction molecule expression is correlating with histological grading. The same is observed for α-2,3,6- and β-1,3,4-Integrins. *Conclusions:* The strength of expression of various molecules in CRC tissue specimens is correlating with histological grading. Up-regulation of expression during tumour suppression is very rare, while down-regulation accompanying increased de-differentiation is the predominant scheme. Only a few molecules studied in this work match valuable prognostic parameters such as TNM-staging or even survival. These could therefore beneficially contribute to the evaluation of the individual tumour patient's prognosis.

729 POSTER

HIGH DOSE 5FU BIOMODULATION BY HIGH DOSE LEUCOVORIN AND INDIVIDUAL 5FU DOSE ADJUSTMENT IN METASTATIC COLORECTAL CANCER. A MULTICENTRIC PROSPECTIVE STUDY OF 130 PATIENTS

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Extrahematopoietic toxic side effects limit 5FU dose intensification. In a previous study with 5FU dose escalation, a pharmacokinetic follow up led us to define a therapeutic index. 5FU plasma level range: 2.5 to 3.5 mg/l (AUC: 20 to 28 mgxh/l (Proc. AACR 92). *Study:* a phase II prospective study was carried out from 05/1991 to 12/1992. Weekly 8 hour infusion high dose 5FU were potentiated by 400 mg/m^2 leucovorin. The initial dose of 5FU, 1300 mg/m^2, was adapted weekly, according to a 5FU plasma levels follow up (HPLC) to obtain the optimal therapeutic range previously determined. The therapeutic efficiency was evaluated after 2 months in the optimal range. *Results:* 130 patients (pts); no prior chemotherapy or only adjuvant chemotherapy (18 pts); mean age 62 (27–75); initial P.S.: 0 (28%); 1 (26%); 2 (36%); 3 (3%). *Metastatic sites:* liver (71%); lung (20%); lymphnodes (8%); other (11%); local recurrence (17%); measurable disease (89%). **Toxicity for the whole treatment** (mean: 9 months (mo); diarrhea (39%) (4 grade III); handfoot syndrome (30%) (4 grade III); mucositis (4%); W.H.O. grade toxicity: I (22%); II (25%); III (3%); IV (0%). *P.S. after 2 months:* improved for 50% pts. *Response rates:* CR (17%); PR (39%); minor + stable disease (29%); progression (15%); mean duration of response (15.5 mo). *Overall survival and disease free survival:* at 1 year (68.5%, 53%); at 2 years (38%, 18%); median survival: 15 mo; mean disease free survival: 11 mo. *Pharmacokinetics Study:* 5FU dose necessary to obtain therapeutic levels: at 3 months (3 g, s.e. 68, 0.9 g to 4.5 g), at 6 mo (3.5 g, s.e. 450, 1 g to 7 g). Five pts were immediately in a highly toxic zone. Time necessary to obtain the therapeutic levels was predictive for the quality of the response (CRvsPR + ST: 3 vs 6 courses). Variations of 5FU metabolism were observed during the treatment leading to a 5FU plasma levels decrease or increase. They required a 5FU dose adjustment to maintain the optimal 5FU levels to prevent tumor escape or acute toxicity. *Discussion:* we have started a multicenter phase III trial comparing a constant dose of 5FU and an individual 5FU dose adjustment to prove the benefit of a pharmacokinetics follow up.

730 POSTER

PRE-OPERATIVE RADIOTHERAPY TO PREVENT LOCO-REGIONAL RECURRENCE IN RECTAL CARCINOMA

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Aim of study: To analyze local control rate and survival of a series of patients included in a phase I–II pilot study.

—Patients and treatment: Between 1980–92, 170 patients were included. Median age: 61 Y, sex ratio: 1.7 M/F. All patients with proven adenocarcinoma (7% poorly differentiated) of the rectum. Clinical stage: T2: 68, T3: 85, T4: 17. After irradiation and surgery pathological staging was: pT0: 24, pT1: 22, pT2: 43, pT3: 73, pT4: 8, pN0: 128, pN1: 42.

Radiotherapy (RX) was given with a patient in the prone position. 3 fields technique 18 MV × rays. Accelerated schedule: 39 Gy/13F/17 days. Surgery performed between 1 to 9 weeks after the end of RX. No chemotherapy.

Results: Median followup: 50 months. Overall survival: 71%, 5 years. Actuarial probability of pelvic relapse 10% 5 years. For pT0-1-2 the local control probability is 96% but T4 have a risk of local relapse of 26%. Local relapse at 5 years is 5% in pN0 but 42% for pN1-2. Overall survival at 5 years is strongly correlated with pN: 87%. pNO vs 36% for pN1–2. In 62% of patients a restorative surgery was possible with a 8% risk of fistula. Operative mortality was 2%. There was no grade 3 radiation late toxicity.

Conclusion: Accelerated preoperative RX limited to the posterior pelvis is well tolerated. It appears to decrease local pelvic relapse and may be to increase the chances of sphincter preserving surgery. Its role on survival is still debated.

731 POSTER

RANDOMIZED TRIAL OF IMMUNOMODIFIER THIABENDAZOLE IN COMBINATION WITH MITOXANTRONE. METHOTREXATE AND FLUOROURACIL CHEMOTHERAPY IN THE TREATMENT OF COLORECTAL CANCER

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A double blind randomized clinical study was started in 1987 on patients with advanced colorectal cancer. 49 patients have been treated with MMF chemotherapy consisting of mitoxantrone 6 mg/m^2, methotrexate 150 mg/m^2 followed by fluorouracil 1000 mg after one hour pause and two 400 mg tegafur or carmofur + citrovorum factor on the next day. Chemotherapy was repeated every 2 weeks except mitoxantrone every 4 weeks. Thiabendazole 200 mg or placebo were given twice daily on days 4–10 of chemotherapy. In the thiabendazole arm there are 2 complete responses, 6 partial responses, 13 stable diseases and 3 disease progression, when the corresponding numbers in the placebo arm are 2 CR, 3 PR, 11 St and 9 PD. Median survival in the thiabendazole arm is 11 months (1.5–66+) and in the placebo arm 6 months (1.5–60+). Three patients have survived over 3 years in both treatment arms. Two of the 3 patients in the placebo arm and 1 of the 3 patients in the thiabendazole arm have been treated with successful additional surgery. All these patients in both arms received either as a maintenance chemotherapy or as a second line chemotherapy daily carmofur + leucovorin. The treatment was tolerable. Grade 3–4 toxicity was not encountered. MMF proved to be efficient in colorectal cancer. 27% of patients responded. Thiabendazole proved to be a safe and nontoxic immunopotentiator. More studies are warranted to evaluate its efficacy in the treatment of colorectal cancer.

732 POSTER

MODULATION OF WEEKLY HIGH DOSE INFUSIONAL 5-FLUOROURACIL (FU) BY LEUCOVORIN (LV), α-INTERFERON (IFN) OR LV PLUS IFN IN ADVANCED COLORECTAL CANCER. RESULTS OF A MULTICENTER RANDOMIZED TRIAL OF THE AIO

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Since 7/92 236 patients (pts) have been randomized to receive FU 2.6 g/m^2 i.v. as 24 h infusion combined with LV 500 mg/m^2 as a 2 h infusion (A), or IFN 3 Mio U s.c. 3×/week (B) or LV plus IFN (C), repeated weekly ×6 with 2 weeks rest. A sequential analysis (J. Whitehead, 1993) for objective response was planned with $\alpha = 0.05/3$, $\beta = 0.2$ to detect a difference of $\sigma = 0.25$ or equivalence. After evaluation of the first 93 pts, randomization to arm C was stopped because of statistically equal response rates (RR) to arm A (A 39%, C 38%) but increased toxicity of C (no toxic death in A and B, 10% in C) (Ann Oncol: 4, 1995). Currently 195 consecutive pts are evaluable:

	NPat	Tox. 3/4°	RR	Resp.duration	TTP
FU_{24h}/LV	73	25%	39%	11.6 mo	6.8 mo
FU_{24h}/IFN	75	11%	22%	8.6 mo	3.8 mo
FU_{24h}/LV/IFN	47	23%	27%	9.3 mo	6.3 mo
p-value		n.s.	<.05	n.s.	<.0003

Diarrhea and mucositis were major toxicities (CTC). Median survival for all pts is currently 14.5 mo. *Conclusions:* Infusional FU/LV is superior to FU/IFN. IFN added to FU/LV does not improve the activity of FU/LV.

733 POSTER

RANDOMISED CLINICAL STUDY OF UKRAIN ON COLORECTAL CANCER

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Results from the National Cancer Institute (Bethesda, U.S.A.) showed that Ukrain (NSC 631570) has on human colorectal cell culture lines a more than 100-fold higher cytotoxic activity than broadly used 5-fluorouracil (NSC 19893). In the EORTC study Ukrain was toxic to the colorectal cell lane CXF. That date gave us the basis for the next clinical study. In a randomised study 108 patients with advanced colorectal cancer, average 61.2 years, were included. 54 patients were treated with Ukrain as monotherapy and 54 with 5-fluororacil. The therapy results (clinical, haematological, immunological, biochemical) show that Ukrain has favourable properties in the treatment of colorectal cancer and clearly show advantages in contrary to 5-fluorouracil. Stability of the disease was reached in 88.8% and only 27.7% in the control group. The pretreatment with Ukrain facilitated the operability of the patients. The malignotoxic action of Ukrain in the clinic is confirmed by the results of pathomorphosis that gives more possibilities in operative treatment and increases the survival rate. Ukrain is a new effective drug in the therapy of colorectal cancer.

734 POSTER

TISSUE LEVELS OF 5,10 METHYLENETETRAHYDROFOLATE AND TETRAHYDROFOLATE IN PTS WITH COLORECTAL CARCINOMA WITH OR WITHOUT PRETREATMENT WITH FOLINIC ACID OR 5-METHYLTETRAHYDROFOLATE

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The modulation of 5-fluorouracil (5-FU) with folinic acid (FA) has been established *in vitro* and in various clinical studies for the treatment of colorectal carcinomas. Although pharmacokinetics and metabolism of FA in serum are well established the dose of folinic acid is still debated. As only few data about tissue levels of the modulating metabolite of FA, 5,10-methylentetrahydrofolate (mTHF), in humans are available, we used the "tritium-release-assay", for evaluation of reduced tissue folate pools in mucosa, primary tumor, liver and liver metastases from pts with colon carcinoma with and without pretreatment with various doses of FA or 5-mTHF. Drugs were given i.v. as short term infusion just before surgery. So far, analysis has been completed in 68 pts (23 mucosa, 22 tumor, 11 liver and 12 metastases) without pretreatment as well as 22 pts after pretreatment with 200 mg/m^2 FA and 20 pts with 5-mTHF, respectively. In both treatment groups reduced folate pools in mucosa and primary tumor were expanded, 5-mTHF however was somewhat less effective than FA. Furthermore, mucosa and tumor tissue was obtained after pretreatment with low dose (20 mg/m^2) and high dose (500 mg/m^2) FA from 10 pts. each treatment group. These specimen are currently under investigation regarding combined pools of mTHF and THF, and data will be presented at the meeting. Supported by DFG grant Ku 753-1/2 and MEDAC GmbH.

735 POSTER

L-LEUCOVORIN (LLV) AS A MODULATOR OF 5-DAYS 5-FLUOROURACIL (5FU) IN ADVANCED COLORECTAL CANCER (ACC): HIGH DOSE (HD) VERSUS LOW DOSE (LD)

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LV has a defined activity in the biochemical modulation of 5FU so that in ACC LV + 5FU is superior to 5FU alone in term of objective response