intraperitoneal chemotherapy. Mean operative times was 323 minutes, and mean blood loss were 1 207 milliliters. There was no mortality. Morbidity was related to four transient biliary leakages. There was no systemic complication due to chemotherapy. Hospital stay was 22 days. After a median follow-up of 14.4 months, there was no detectable recurrence of the peritoneal carcinomatosis. At the end of the study, seven patients were disease free. When minimal or moderate peritoneal carcinomatosis is detected during hepatic metastasectomy, the association of a hepatectomy with complete cytoreductive surgery of peritoneal carcinomatosis immediately followed by intraperitoneal postoperative chemotherapy is logical, and safe. This agressive treatment is well tolerated, although the frequency of biliary leakages is higher than after standard hepatectomy. Absence of peritoneal recurrence, and rate of survival are promising.

744 POSTER

Biological factors predicting the outcome of regional chemotherapy in colorectal carcinoma metastases to liver

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Purpose: Regional intrahepatic chemotherapy may be beneficial for selected subgroup of patients with liver metastases of colorectal carcinoma. However, biological criteria precising indications to this demanding type of treatment have not yet been established.

Methods: Twenty two cases of colorectal carcinoma metastases to liver treated by regional chemotherapy were analysed for DNA ploidy and PCNA, Ki67, p53, p21 (WAF1), mdm2, c-erb2, CEA, CA19-9 and P-glycoprotein (MDR) expression and results related to survival.

Results: Mean survival of patients with DNA diploid tumors was significantly longer (20 versus 11 months, P = 0.04) comparing to DNA aneuploid ones. Only the trend for lower PCNA positivity and p53 expression could be observed among DNA diploid tumors. All p53 positive cases were negative for p21 (WAF1) and mdm2. Other parameters were unrelated to outcome of treatment.

Conclusion: DNA ploidy, perhaps together with p53 overexpression and PCNA positivity, may be predictive of effectiveness of regional intrahepatic chemotherapy performed for colorectal cancer liver metastases. However, a larger study is needed to confirm these preliminary findings. (Supported by IGA MZ CR grant No.2923-3)

745 POSTER

Infusional 5-fluorouracil with and without calcium-folinat as second line therapy in advanced colorectal cancer – A retrospective cohort study of different protracted infusion regimens

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Purpose: Biomodulation of 5-Fluorouracil (5-FU) with Calciumfolinat (CF) in bolus regimens increases response rates, and probably survival rates of patients with advanced colorectal cancer (CRC). The benefit of CF in second line protracted infusional protocols of 5-FU is not so clearly defined. Consequently we compared the outcome of two infusional 5-FU regimens with and without CF.

Methods: Fifty-eight patients with CRC were treated from May 1991 until September 1996 with two different second line infusional 5-FU protocols after failure of CF-modulated 5-FU – bolus regimens (380–450 mg/m^2 5-FU + 20–200 mg/m^2 CF d1–5 q 4w). Twenty-eight patients received 60 mg/kg 5-FU alone as a 48 hours infusion with ambulatory pumps every week until progression. Thirty patients were treated with 500 mg/m^2 CF as a 2 hours infusion followed by 2600 mg/m^2 5-FU as a 24 hours infusion every week with a third weeks rest until progression. Kaplan-Meier survival analysis and the log-rank-test were applied.

Results: The two cohorts were adequately matched in respect of age, tumor load, and time to progression after first line therapy, and received a mean of 27 resp. 14 cycles. The CF-scheme exhibits higher response rates but more toxicity. Median survival times (30 resp. 46 months) were significantly different (p = 0.09).

Conclusions: CF modulation of 5-FU in protracted infusional protocols as second line therapy increases response rates and survival rates of CRC patients.

746 POSTER

Oxaliplatin (LOHP) and 5-fluorouracil (5-FU) synergism in advanced colorectal cancer patients (ACRC)

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Previous in vitro and in vivo studies reported LOHP and 5-FU synergistic effect in ACRC. We studied their combination in 5-FU refractory ACRC. **Pts and Methods:** pts had high dose 5-FU-folinic acid (FA) refractory ACRC (progressive disease while on 5-FU-LV treatment). LOHP was added, at 130 mg/m^2/3 weeks by IV infusion over 2 hours, to unchanged 5FU-LV schedule, 1.3 g/m^2 weekly 5-FU, plus 400 mg/m^2 FA.

Results: 38 patients from 6/94 to 5/96, with measurable disease in all pts. Mean age: 64; PS: 0 (15), 1 (15), 2 (7), 3 (1), sites involved: liver: 27, lung: 7, peritoneum carcinomatosis with measurable mass: 10, lymphnode: 1, number of sites involved: 1 site: 26, 2 sites or more: 12; previous radiotherapy: 9; mean duration of 5-FU-LV-LOHP: 4 cycles (1 to 12). WHO toxicity was: neuropathy: 56 GI, 15 GII, in 22 pts; neutropenia: 10 GI, 4 GII, 2 GIII in 7 pts; thrombopenia: 8 GI, 6 GII, 4 GIII in 8 pts; diarrhea 15 GI, 18 GII, 6 GIII in 14 pts; 8 pts (21%) had grade III toxicity. Responses (WHO): 14 PR (36%), 14 SD, and 10 PD after 3 cycles of LOHP-based treatment; mean duration of the response: 6 mths (1 to 11), median Progression Free Survival: 5.5 mths, median Overall Survival: 7.6 mths, 9 pts were alive at +12 mths.

Discussion: LOHP-5-FU-LV have synergistic activity; toxicity is mild; response rate appears to be higher than expected with LOHP alone in 5-FU refractory ACRC. This combination merits further investigation in first line chemotherapy.

747 POSTER

Biweekly administration of methotrexate (MTX), levofolinic acid (LFA), and 5-fluorouracil (5-FU) in advanced colorectal carcinomas

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Background: In a previous phase II study, 54 colorectal cancer patients (pts) received biweekly MTX (500 mg/m^2) 24 h before 5-FU (600 mg/m^2) + LFA (250 mg/m^2) administration. A 26% ORR was observed in chemo-naive pts.

Purpose: To test whether higher MTX and 5-FU doses could improve the ORR without increasing the acute toxicity.

Methods: Patients with advanced colorectal cancer received MTX 750 mg/m^2 on d 1 followed 24 h later by 5-FU 800 mg/sqm and LFA 250 mg/m^2 every 2 weeks until PD or for a maximun of 16 courses.

Results: As of Jan 97, 100 pts were enrolled and 90 pts (48 chemo-naive, 42 pretreated) were evaluable for response (10 pts were too early), according to intention-to-treat analysis. Overall, 25 pts achieved a response: 19/48 (40%, 95%CI = 26–55) chemo-naive and 6/42 (14%, 95%CI = 5–29) pretreated pts. Toxicity: the treatment was usually well tolerated, but 3 treatment-related deaths and 4 early withdrawals for toxicity occurred. Only 2/7 of these events were observed in chemo-naive pts. Grade 3–4 mucositis and diarrhoea occurred in 12% and 9% of courses, respectively, and were less frequent in chemo-naive pts. Grade 4 neutropenia and thrombocytopenia each occurred in less than 5% of courses.

Conclusions: The biweekly administration of MTX followed by 5-FU+LFA is a well tolerated treatment for colorectal cancer pts and it shows a very interesting activity both in chemo-naive and pretreated pts.

748 POSTER

Insulin-like growth factor binding protein-3 (IGFBP-3) proteolysis in patients with colorectal cancer: A possible early prognostic factor of metastatic progression

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Purpose: The Insulin-like Growth Factor (IGF) system plays a key role in intestinal epithelial cell functions and colorectal neoplastic growth. In human,

the limited proteolysis of IGF Binding Protein-3 (IGFBP-3) increases the tissue bioavailability of IGFs, in response to a catabolic stress. The aim of this prospective study (2 years), in 14 colorectal cancer patients was to assess if postoperative induction of IGFBP-3 protease activity may be a prognostic marker of metastatic progression.

Methods: Serum samples were taken before (J0) and after (J6) surgery and analyzed by Western Blot.

Results: Before surgery, we observed a strong increase in IGFBP-2 (+340%) associated to a slight decrease in IGFBP-3 levels whereas IGFBP-3 protease activity was not significantly altered. After surgery, two different profiles were noted: a/ in 7/14 patients, we observed an expected catabolic profile with induction of IGFBP-3 protease activity associated to diminished IGFBP-3 and increased IGFBP-2 concentrations. No metastatic disease was observed in this group. b/ in 7/14 patients, no significant proteolytic mobilization of the IGF system was observed. 4/7 patients had a progression. We hypothesize that such a metabolic anergy could be related to the postoperative persistence of cancer cells that released an IGFBP-3 protease inhibitor. Such an inhibitor was indeed found in conditioned medium from HT29-D4 human colon cancer cells.

Conclusion: Assessment of IGFBP-3 protease activity in postoperative serum might be an useful early prognostic factor of metastatic progression in colorectal cancer patients.

749 POSTER

Diagnostic and prognostic significance of protein patterns in human epithelial cancer

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To improve results of surgical therapy of human epithelial tumors, new diagnostic, prognostic and therapeutic markers are necessary. Available staging systems (e.g. TNM-system) are clinically useful but show severe limitations in defining the prognosis of a particular patient. New approaches, close to the clinical reality, relying on phenotypic patterns are emerging. These markers can be searched by differential display techniques at DNA (PCR), RNA (RAP-PCR) or protein (high-resolution 2-dimensional polyacrylamide electrophoresis) level. The accuracy of such phenotypic comparisons between pathological and normal tissues depends on the purity of the samples.

We have developed techniques of preparation of pure epithelial cell samples from fresh operation specimens without any enzymatic digestion.

Using these techniques, followed by denaturation, gel running, protein microsequencing and immunoblotting, a protein map (master) of the normal colonic mucosa was defined with over 50 reference landmarks and will soon be available on the Internet (http://www.expasy.ch) and can be matched with pathological patterns obtained with these reproducible techniques.

750 POSTER

Safety of adjuvant mAb 17-1A in colorectal cancer (CRC)

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Purpose: Monoclonal antibody (mAb) 17-1A (edrecolomab) has reduced distant metastases and mortality as adjuvant treatment in CRC Stage III (Riethmüller et al , Lancet 343, 1994; Proc. ASCO 15, 1996). After German marketing authorization, a surveillance trial started in 1995 to monitor safety in clinical use.

Methods: 277 patients (52% male, 48% female; age 64 y [35–85]; Stage [I–IV]: 1.5, 19.4, 72.5, 6.6%) were treated with 17-1A.

Results: 142 pts (51.3%) showed no adverse effects. 103 pts (37.3%) developed toxic effects grade 1–2; 21 pts (7.6%) grade 3 and 11 pts (4%) grade 4, requiring discontinuation of 17-1A and symptomatic treatment with full recovery. No lethal toxicity was observed.

WHO-grades (% patients)	0	1	2	3	4
Nausea	79.8	12.3	6 1	1.8	–
Vomiting	92.1	4.7	2.5	0.7	–
Diarrhoea	69.3	13.7	12.3	2.9	1 8
Abdominal pain	81 2	11.9	3.6	2.5	0.7
Flush/Erythema	91.7	4.0	2.5	1.1	0.7
Anaphylactic reaction	97 1	0 7	1.1	0.4	0.7

Conclusion: Adverse effects were predominantly mild to moderate with the exception of a minority of pts (11.6%) developing grade 3–4 gastrointestinal or anaphylactic reactions. Toxicity observed in this large cohort is in accordance with previous reports and underlines the favourable safety profile of 17-1A.

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751 POSTER

Adjuvant chemotherapy of Dukes C colon carcinoma: Comparison of 5-FU + levamisole (LEV) 12 months vs. 5-FU + folinic acid (FA) 12 months VS 5-FU + FA 6 months

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Purpose: Postoperative chemotherapy has been established for stage III (Dukes C) colon cancer. Currently, treatment with 5-FU and LEV for 12 months is still considered standard outside clinical studies. However, optimal duration of therapy and biomodulation of 5-FU with FA might improve adjuvant treatment.

Patients and Method: From 1993 until 1996 116 patients with surgically resected colon cancer (Dukes C) were randomly assigned to A) standard therapy with 5-FU + LEV for 12 months, B) FA 100 mg/m^2 + 5-FU 450 mg/m^2, day 1–5 every 4 weeks for 12 cycles and C) 5-FU + FA 6 cycles respectively.

Results: After a median follow-up of 3.2 years no significant difference concerning disease free survival (p = 0.7) and survival (p = 0.6) was observed. Toxicity among the 3 groups is similar. However, a trend for more pronounced gastrointestinal toxicity under treatment with 5-FU + FA is observed.

Conclusion: In accordance with recently presented results of other studies, the preliminary data of this trial indicate that adjuvant treatment with 5-FU + FA for 6 months may be as effective as treatment with 5-FU + LEV for 12 months.

752 POSTER

Brain metastases from colon- and rectumcarcinoma

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Purpose: We analyzed 20 cases with respect to pattern of spread and prognosis after radiotherapy (RT) or neurosurgery plus radiotherapy.

Methods: 14 patients were treated with RT (30–60 Gy), 6 with neurosurgery plus radiotherapy (OP + RT, 30–40 Gy). All had advanced primary tumors (T3, T4), most of which were poorly differentiated; lymph node metastases were common. In 5 cases the brain was the first site of distant metastases. Ten patients had a solitary brain metastasis.

Results: Results of OP + RT were superior to those of RT, with respect to palliation of symptoms as well as to local tumor remission and survival. Overall median survival was only 51 days (1-year survival rate 6%). In 5 of 14 cases symptomatic improvement was observed after RT. Partial remission of the brain metastases occurred in 3 of 14 cases. The presence of extracerebral metastases was the most important prognostic factor.

Conclusion: Selected patients considered to have a favourable prognosis may profit from combined treatment (OP + RT). Despite the short survival time, stereotactic irradiation should be evaluated as an alternative to conventional RT in the remaining patients because the palliative effect of RT was relatively disappointing.

753 POSTER

Pseudocontinent perineal colostomy following abdominoperineal resection: Technique and findings in 40 patients

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Purpose: This prospective study was designed to evaluate the morbidity and the functional results of pseudocontinent perineal colostomy with free flap of colic muscle following abdominoperineal resection.

Methods: Forty patients (26 men and 14 women) averaging 50 of age were given this type of treatment between February 1989 and February 1997 at the Gustave-Roussy Institute. Thirty-four patients presented with