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

P. Klefström, J. Seiro, M. Turunen, S. Ignatius
Deaconess Medical Center, Helsinki, Finland

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

C.H. Köhne, P. Schöffski, H. Wilke, C. Käufer, H. Rauschecker, R. Andreesen, U. Ohl, H.J. Lange, U. Klaassen, M. Westerhausen, W. Hiddemann, G. Schott, J. Bade, G. Strohmeyer, U. Schubert, H. Hecker, H.J. Schmoll
Hannover Medical School, Department Hematology/Oncology, D-Hannover, Germany

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

Y.M. Susak[1], O.Y. Yaremchuk[1], V.S. Zemskov[1], O.B. Kravchenko[1], A. Liepins[2], I.M. Yatsyk[1], O.B. Korsh[3]
[1] Ukrainian State Medical University, Department of General Surgery and Oncology
[2] Memorial University of Newfoundland, St. John's, Newfoundland, Canada
[3] Ukrainian Anti-Cancer Institute, A-1040 Vienna Austria

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

M. Kühl[1], K. Jauch[1], J. Rauch[1], B. Engemann[1], C. Riedelsheimer[1], A. Schalhorn[1,2], W. Wilmanns[1,2]
[1] Ludwigs-Maximilians-University Munich, Germany
[2] Gesellschaft für Strahlen-und Umweltforschung (GSF), Germany

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)

R. Labianca, S. Cascinu, S. Barni, G. Fiorentini, L. Frontini, G. Comella, A. Zaniboni, G. Dallavalle, G. Pancera, A.C. Luporini, A. Pessi, G. Luporini
GISCAD (Italian Group For the Study of Digestive Tract Cancer) (Sponsored by CNR n. 93.02362.PF 39)

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

(O.R.); the 5 days regimen with LD-LV appears active as HD-LV weekly administered.

In this multicentric phase III study from 11/91 to 6/94, 422 patients (pts) were randomized between LLV 100 mg/sqm/iv × 5 d (arm A) versus LLV 10 mg/sqm/iv × 5 d (arm B). All pts received 5FU: 370 mg/sqm/iv × 5 d. Treatment was recycled every 28 d. Toxicity was acceptable in both groups with only 11% of pts experiencing grade 3–4 diarrhea and mucositis. At a median follow-up of 18 m, of 372 pts evaluable we observed similar activity: 20 OR (10.6%) in arm A (3 of them complete) and 21 (11.4%) OR in arm B, with 4 CR. No differences were observed in overall survival: 10 m for both groups. In this study HD-LLV and LD-LLV appear equally active in biochemical modulation of 5-d 5FU with lower costs for LD-LLV.

736 POSTER

P53 PROTEIN EXPRESSION IN COLORECTAL CANCER

G. Lanza Jr, I. Maestri, A. Santini, A. Dubini, R. Gafà, L. Cavazzini
Department of Pathology, University of Ferrara
Division of Medical Oncology, St. Anna Hospital, Ferrara, Italy

p53 protein expression was examined in 204 surgically removed colorectal adenocarcinomas by immunohistochemistry using frozen tissue sections and monoclonal antibody DO7. Nuclear staining of more than 5% of neoplastic cells was observed in 124 (60.8%) tumours, which were classified as p53 positive. p53 immunoreactivity was found to be unrelated to several clinical and pathological variables, including age and sex of patients, tumour site, tumour stage and grade of differentiation. p53 expression was demonstrated to be closely related to the flow cytometric nuclear DNA content of the tumour. DNA diploid carcinomas and aneuploid tumours with DNA index (DI) ≤ 1.20 had similar frequencies of p53 positive staining (40.9% and 48.1%, respectively), whereas aneuploid carcinomas with DI >1.20 had a significantly higher frequency of p53 overexpression (69.6%) ($P = 0.0003$). With respect to the total study population (mean follow-up 20.6 months; range, 9–35 months) the duration of overall survival was independent of p53 expression. However, in the group of 141 patients with TNM stage I–II–III disease who had undergone curative resection, positive p53 staining was associated with poorer disease-free ($P = 0.076$) and overall survival ($P = 0.025$). Our results provide supporting evidence that p53 expression may represent an independent prognostic parameter in colorectal cancer.

737 POSTER

ACUTE TOXICITY OF THE COMBINATION OF POSTOPERATIVE CHEMOTHERAPY (5FU-FOLINIC ACID) AND RADIOTHERAPY IN PATIENTS WITH RECTAL (DUKE'S B2, C) NON-METASTATIC CARCINOMA

Ch. Latoufis, J. Katsilieris, E. Marangoudakis, K. Kyriakopoulos, E. Kakouris, K. Kyrisonis, E. Manousakis, P. Christoforidis, N. Ntanos
"ELPIS" General Hospital, Athens, Greece "St. SABBAS" Anticancer Hospital, Athens, Greece

The aim of this study is the evaluation of the acute toxicity of chemotherapy and radiotherapy when they are combined postoperatively in patients with non-metastatic rectal carcinoma, stage B2, C or in early local recurrence. Thirty-six patients were studied (20 males, 16 females, medium age 63 years). They all had been radically operated and were treated with a combination of six cycles of chemotherapy (5 FU + folinic Acid) and radiotherapy (XRT). Two cycles of chemotherapy were given prior to XRT, two cycles during XRT and two cycles thereafter. The medium XRT dose range was 5040 cGy while the medium 5FU dose range was 400 mg/m^2 and the folinic acid dose was 30 mg/m^2. The patients were analysed for acute toxicity during the treatment and up to 3–6 months after it was completed. The following specific symptoms were evaluated to determine the tolerance of the treatment: Diarrhea, nausea, stomatitis, leucopenia, thrombocytopenia, anaemia.

Results:

Diarrhea	Moderate	24/36	66.6%
	Severe	5/36	13.8%
Nausea	Mild	3/36	8.3%
Stomatitis	Mild	12/36	36.1%
Stomatitis	Moderate	10/36	28%
Leucopenia	Mild	7/36	19.4%
Thrombocytopenia	Mild	1/36	2.7%
Anaemia	Mild	2/36	5.5%

In conclusion the combination of postoperative chemotherapy and radiotherapy in patients with locally advanced (Duke's B2, C) or recurrence carcinoma of the rectum is well tolerated and easily implemented even in elderly patients.

738 POSTER

OXALIPLATIN (L-OHP®): SUMMARY OF RESULTS IN ADVANCED COLORECTAL CANCER (ACC)

F. Lévi[1], D. Machover[1], M. Marty, E. Diaz-Rubio[2], A. de Gramont[3], C. Garufi[4], M. Itzhaki[1], E. Cvitkovic[1], M.A. Bensmaïne[1], S. Brienza[5], J.L Misset[1]
[1] Hôp. p. Brousse, Villejuif, France
[2] Hospital Salt Carlos-Madrid, Spain
[3] Hôpital St Antoine, Paris, France
[4] Istituto Regina Elena, Rome, Italy
[5] Debiopharm, Villejuif, France

Standard treatment of ACC consists of a combination of 5-fluorouracil (5-FU) will folinic acid (FA). No other cytotoxic agents tested so far showed therapeutic benefit in the treatment of ACC. L-OHP® showed activity in 6/8 colon cancer lines in the NCI compare screen. It was tested after an *in vivo* (L1210) demonstration of synergistic effect with 5-FU and the observation of one partial response in a phase 1 study. Nine clinical trials with L-ODHP® (2 hr bolus or 5-day flat (F) or chronomulated (CM) infusion) in 582 pts with ACC have been conducted between 03/88 and 06/94: 3 phase II in monotherapy (138 pts), 4 phase II (159 pts) and 2 phase III (278 pts) in combination with 5-FU/FA. Significant results observed are:

- The toxicologic profile of L-OHP® (no renal or hematologic toxicity) allowed a safe association with 5-FU and FA.
- Peripheral sensitive neuropathy was dose-limiting: grade III (functional impairment) occurred after a median of 6 courses (780 mg/sqm) in 10% of the patients. Its usual reversibility and its easy follow-up limited the extent of this drawback.
- Oxaliplatin showed intrinsic activity in pretreated and 5-FU resistant ACC. The three phase II studies showed respectively 10%, 11% and 10% response rates in 29, 58 and 51 patients (14/138 with overall response rate (ORR) = 10%).
- Four studies, combining L-OHP with high dose 5-FU/FA (2-day q 14d F schedules or 5-day q 21d CM schedules) achieved high activity (ORR = 39%—42/108 pls) in 5-FU/FA pretreated patients. PFS and survival were respectively 10 and 17 months.
- In one sequential study, in 25 INS resistant (20 PD-5 SD) to CM 5-FU/FA, the addition of L-OHP7reg; induced a 29% response rate. This point suggests a clinical synergistic effect with 5-FU/FA in humans.
- Clinical synergism between L-OHP® and 5-FU/FA was further suggested by a 51% ORR obtained with chronomodulated 3-day delivery in 138 pts with previously untreated metastatic colorectal cancer. In these European trials, median progression free survival and survival were respectively 10 and 17 months, and largely exceed those usually obtained with 5-FU/FA.

Conclusion: L-OHP® was active against clinically resistant ACC. When combined with high-dose 5-FU/FA, it allowed to apparently achieve highest antitumoral activity, PFS and survival in a multicenter setting.

739 POSTER

FLUOROURACIL (FU) AND FOLINIC ACID (FA) ALONE OR WITH ALPHA-2B INTERFERON (IFN) IN ADVANCED COLORECTAL CANCER (ACC). A MULTICENTRIC RANDOMIZED STUDY OF THE SOUTHERN ITALY ONCOLOGY GROUP (GOIM)

G. Colucci, E. Maiello, V. Gebbia, G. Serravezza, S. Palazzo, F. Giuliani, G. Lelli, G. Pezzella, S. Cariello, A. De Mitrio, G. Pacilio, N. Gebbla
Department Medicine, Oncology Institute of Bari and Goim, Italy

To evaluate the possibility that a low modulating dose of IFN can enhance the anti-tumor effect of FA-FU combination therapy, patients (pts) with ACC were randomized to receive either FA (I-isomer form) 100 mg/m^2 iv just before FU 375 mg/m^2 iv for five consecutive days alone (A), or with IFN-alpha2b 3 MU for seven consecutive days, starting two days before FA-FU administration (B). Both regimens were repeated every three weeks. Two hundred-three pts were entered in the study. Actually, 156 (79 arm A, and 77 arm B) are evaluable for response, and 23 are early to evaluate.

The main characteristics of the evaluable pts were: sex (M/F): A:48/31, B:46/31; median age (A/B): 64/62 yrs; primary tumor site