(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

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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

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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)

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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)

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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