(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

(colon/rectum): A:43/36, B:51/26; metastatic sites (A/B): liver 61/62, lung 13/16, lymph node 15/14, multiple sites 39/35. Tumor response rates (CR + PR) were 23% in the FA-FU group (1 CR, 17 PR; 95% CI: 17%–32%), and 30% in the FA-FU + IFN group (5 CR, 18 PR; 95% CI: 20%–40%). No significant difference was found in overall response rate between the two arms. A total of 180 pts (A:88; B:92) are evaluable for toxicity; grade 3–4 toxicity (WHO criteria) were (A/B): leukopenia 2%/1%, diarrhea 8%/22%, mucositis 5%/12%, nausea and vomiting 2%/7%. Our preliminary results shown better response rate in FA-FU + IFN arm, but a more severe (grade 3–4) gastrointestinal toxicity.

740 POSTER

CYTOGENETIC ANALYSIS IN ADVANCED COLORECTAL CANCER

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We analyzed short term cultures from tumor material of 26 patients with advanced colorectal carcinomas. Clonal anomalies were found in 20 patients. Five tumors showed only slight numerical changes (+7, −Y in 2/5 pt). The remaining 15 tumors had highly complex karyotypes. Structural aberrations affected all chromosomes, except Y. The most frequently rearranged bands were 5q21, 7p15, 9p21, 13q11, 16p12, 17p13, 18q21, 21q11. Anomalies of chromosomes 5, 17 and 18 occurred concomitantly in 9/20 patients. Tumors of the proximal colon (n = 6) were with one exception diploid or near diploid and showed no particular pattern of aberrations. All patients with deletions of 17p (n = 6) had near tetraploid karyotypes with high cell to cell variability and a median of 9 structural aberrations ($P < 0.05$); 4 of them presented with parenchymal metastases. The tumor karyotypes of patients with hepatic metastases at the time of surgery (n = 6) revealed a trend to more numerical and structural aberrations (8 structural aberrations in median, versus 3). Changes involving 8p22 or loss of 8 were found in tumors of all parts of the colon and potentially associated with an unfavorable prognosis (4/6 deceased patients). A deletion in 16p12 was found in 4 patients with advanced tumors, three of them in patients with tumors of the proximal colon.

741 POSTER

BRAIN METASTASES IN COLORECTAL CANCER: AN UNUSUAL METASTATIC SITE. REPORT OF 15 CASES TREATED WITH RADIOTHERAPY

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From August 1991 to November 1994, we observed brain metastasis in 15 pts with colorectal cancer (CRC):4 Males/11Females, median age 59 y (43–69), CRC staging 7B, 4C, 4D. Treatment of the primitive tremor consisted with surgery (8 pts) plus chemotherapy (CT) (4 pts) or radiation therapy (RT) (3 pts). 12 pts developed non CNS metastases mostly, hepatic and/or pulmonary (9 pts). 3 pts had isolated CNS metastases. Median time to first metastasis was 18 months (0–66) and median time to CNS metastases was 27 months (1–129). CNS treatment was RT (36 Gy) in all pts, 2 had a previous surgical excision. 10 pts died of CNS metastases, 3 pts of other metastases ± local recurrence. Median survival time was 3 months (0–17). 2 pts are alive with disease at 2 and 17 months. Brain metastases, classically unusual In CRC become more frequent, potentially because of the wider use of systematic CT. Despite RT, their prognosis remains very poor.

742 POSTER

PATHOPHYSIOLOGY AND THERAPY OF IRINOTECAN (CPT-11) INDUCED DELAYED ONSET DIARRHEA (DD): A PROSPECTIVE ASSESSMENT

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DD is the main toxicity of CPT-11 at the currently recommended dose (RD) of 350 mg/sqm IV (30′) q 3 weeks. In previously treated colorectal cancer patients (pts), we tried to determine the mechanism of DD and assess the efficacy of combined antidiarrheal medication. From Dec 93 until March 95, 24 pts having failed $\geq 1 \leq 3$ lines of 5-FU based treatment, entered a CPT-11 Phase II trial at the above RD. In the first cohort (14 pts), Acetorphan (Acet), a specific enkephalinase inhibitor, was given as 100 mg tid PO after the second loose stool, and supplemented, if DD > 48 hrs, with Loperamide (Lop) 2 mg q 2 hrs PO till 12 hrs after last loose stool. Pts had at baseline and if DD occurred endoscopy, with biopsies for Topo I and CPT-11 assays as well as transit time, stool frequency, weight, culture, electrolytes, osmotic gap, pH, fat and protein excretion, α1 antitrypsin (α AT) clearance, D-xylose test; blood tests for VIP, glucagon, somatostatin, gastrin. Twelve/14 pts (first cohort) had CFT-11 DD: 5 responded to Acet alone, and the other 7 responded within 24 hrs to addition of Lop. Transit time normal in 5/7 pts, α AT increased in 4/4 pts. Stools weight >800 gr/day and fecal Na/K increased in 6/6 pts. Osmotic gap small in 3/6 pts. The second cohort (pts 15–25) received simultaneous Acet/Lop after first DD loose stool. Eight/11 pts had DD, and 7/8 had resolution of diarrhea within 12 hrs of treatment start. Available PK's of CPT-11 and SN-38 (active metabolite) show no pharmacodynamic relationship. Results suggest that CPT-11 DD is due to a secretory exudative mechanism, as attested by its response to early simultaneous antisecretory medications.

743 POSTER

PREOPERATIVE RADIATION DOSE ESCALATION ± CHEMOTHERAPY FOR ADVANCED RECTAL CANCER

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Purpose: To assess the influence of preoperative radiation does escalation ± concurrent chemotherapy in patients with advanced rectal cancer. *Methods:* Patients with clinical T3/T4 rectal cancer received preoperative XRT ± chemotherapy, followed by surgery. 74 patients received 45 Gy XRT (low-dose group). 82 patients received 55.8 Gy XRT (high-dose group). 33 patients received 55.8 Gy XRT with concurrent 5-FU chemotherapy (CRT group). The 3 groups were compared with respect to post-radiation pathologic stage, local tumor control (LC), disease-specific survival (DSS), freedom from distant metastasis (FDM), and acute toxicity. *Results:* The high-dose XRT and CRT groups had significantly fewer pT3/4 tumors relative to the low-dose XRT group (53% and 51% vs. 70%, respectively, $P < 0.03, \chi^2$). The proportion of pT3/4 tumors in the high-dose XRT and CRT groups was the same, despite the fact that there was a larger proportion of clinically fixed (unresectable) tumors in the CRT group (43% vs. 76%, respectively, $P < 0.005, \chi^2$). The proportion of pN+ patients and the 5-year actuarial LC, DSS, and FDM rates were not significantly different between the groups. There was a significant increase in Grade 3 GI toxicity in the CRT group (24%) vs. the low-dose and high-dose XRT groups (5% and 6%, respectively, $P > 0.005, \chi^2$.) *Conclusions:* The addition of 5-FU chemotherapy to preoperative XRT results in greater downstaging of clinically fixed tumors than XRT alone. The acute toxicity of CRT is greater than that of XRT alone. Patients with clinically fixed rectal cancer benefit most from preoperative CRT.