41 pts (21.5%) experienced grade 3–4 toxicities in arm A versus 18 pts (9.2%) in arm B, $P = 0.0004$. grade 3–4 toxicities (%) were in arm A: neutrophils 7.9 platelets 1, nausea 2.6, diarrhea 4.7, mucositis 9.9, alopecia 1, skin 0.5 and in arm B: neutrophils 2, platelets 0.5, nausea 3.1, mucositis 1.5, alopecia 0.5, skin 0.5. Treatment was stopped in one patient in arm A and 3 in arm B who experienced angina pectoris.

We conclude that the bi-monthly combination of 5FU bolus and continuous infusion with high-dose folinic acid is more active and less toxic than monthly 5 day course of bolus 5FU with low dose Leucovorin.

703 POSTER

CRYOSURGERY OF NON RESECTABLE MALIGNANT LIVER TUMOURS

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The aim of this study was to determine the real place of cryotherapy in the therapeutic strategy of liver tumours. From Oct 1993 to July 1994, 41 patients (pts) have been treated by cryotherapy at our institution, either as a single treatment (Group 1–11 pts), as combined with partial resection (Group 2–19 pts) or as complementary to a complete resection with no sufficient margin of normal liver around the tumour (Group 3–11 pts). There were 7 hepatocellular carcinomas all with underlying cirrhosis, 25 metastases of colorectal cancer and 9 metastases of other malignant tumours. We used the LCS 2000 device (Cryogenic Technology) designed specifically for hepatic cryotherapy. There were 2 per-operative complications related to the procedure: 1 rupture of the tumour and 1 perforation of the liver capsule, both easily controlled by suture. Operative mortality within 2 months was 2.4% (1/41), unrelated to cryotherapy (cardiac infarct at day 3). Serum transaminases increased post operatively in relation to the duration of cryotherapy and the number of treated lesions (Mean maximum value AST: 799 IU/L (Range 78–2541), ALT 802 IU/L (Range 106–1902)). They normalized within 5 days. In Group 1 (Cryo alone), a reduction of tumour size was observed in 4 pts (36%), with disappearance of a treated lesion in one case. Tumour markers were decreased in 3/4 pts with preoperative increased levels. In Group 2 (Cryo + Resection), a reduction in cryotreated tumour size was observed in 6 pts (32%). Decreased tumor markers were demonstrated in 4 cases (21%). In Group 3 ("Adjuvant" cryotherapy), no tumor recurred at the site of cryotherapy. When increased, tumor markers decreased in all cases. Overall, the main determinants of recurrence following cryotherapy were maximum tumour size >5 cm and number of lesions >3.

Conclusion: Cryotherapy is a simple and safe procedure. Objective criteria of anti tumoral effects are demonstrated but need confirmation with a longer follow-up. Selection of pts should exclude all those with large multinodular tumours.

704 POSTER

LOCAL EXPRESSION OF CYTOKINES IN HUMAN COLORECTAL CARCINOMA

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Cytokines locally expressed in cancer may regulate anticancer response and could be autocrine growth stimulators. To characterize the local immune situation in colorectal cancer, constitutive expression of cytokine mRNAs has been investigated in tumor specimens (central and peripheral), normal mucosa and peripheral blood mononuclear cells (PBMC) in 12 patients underwent surgical resection. mRNA for interleukin (IL)-2, IL-4, IL-6, IL-10, IL-2R (p55), CD3, and β-actin as positive control was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) technique, using 1 μg of total RNA for reverse transcription and 28 or 30 cycles of cDNA amplification with specific primer pairs.

Results: 70% of cases constitutively expressed mRNA for 1L-6 in tumor tissues but not in normal mucosa; only in one case IL-6 was expressed both in tumor and in normal mucosa. mRNA for IL-2R (p55) was found in 50% of tumors and in no specimen of normal mucosa. No expression of IL-2 and IL-4 mRNAs was detected at local site. IL-10 was variably expressed at low levels in tumors, normal mucosa and PBMC. CD3 expression was not associated with differences in cytokine gene expression. These findings may be relevant for better understanding the role of cytokines at the tumor site. IL-6 is known to be involved in cancer proliferation as an autocrine stimulator: it seems that oncogenes and oncosuppressor genes are involved in the modulation of its expression in some neoplasms. The present study will be also developed in this direction. Supported by: C.N.R. Targeted Project "ACRO".

705 POSTER

DOXIFLURIDINE IN PATIENTS WITH 5-FU RESISTANT COLORECTAL CANCER

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5-FU is considered the most active drug in metastatic colorectal cancer, but many pts do not respond to this treatment and some even progress, so the development of a second line therapy is an important aim. We set out to determine the activity of oral and i.v. doxifluridine (5-dFUR), a fluoropyrimidine synthesized by Cook in 1976, in pts with metastatic or advanced measurable colorectal cancer who had previously received a 5-FU based regimen at an adequate total dosage (no less than 3700 mg/m^2). Only 48 of the 118 pts treated with 5-dFUR were considered 5-FU resistant according to our strict criteria of documented tumor progression during 5-FU therapy (adjuvant setting or metastatic line) or within 8 weeks of the last administration. The 48 pts received: either 5-dFUR 3000 mg/m^2 as a one hour i.v. infusion on combined with levo-leucovorin 25 mg/dose i.v. days 1→5 every 3 wks (14 pts) or 5-dFUR 6000 mg/m^2 p.o., for 5 days every 10 days and levo-leucovorin 25 mg/dose 2 hrs before 5-dFUR (34 pts). The characteristics of the pts were: M/F 26/22; median age 56 yrs; PS 0–1/2: 34/14. The WHO response rates were 12% PR (4/34) in the group treated per os, and 29% (4/14) in the group treated i.v. The median duration of response in the p.o. and i.v. group was respectively 6 (range 3–11+) and 5 mos (range 3–5+). Responses were achieved by pts pretreated with a median of 9250 mg/m^2 (range 3700–18650) of 5-FU. No WHO grade IV toxicity was observed, whereas grade III diarrhea in 15% of the orally treated group in 15% and 25% of the i.v. group. The encouraging response rate seems to suggest that 5-dFUR is an effective and well tolerated second line therapy for 5-FU resistant colorectal cancer. The incomplete clinical cross-resistance between 5-FU and 5-dFUR has prompted us to plan a further cross-over study to verify this observation. *Data management by I.T.M.O. (Italian Trials in Medical Oncology) Scientific Service.*

706 POSTER

CLINICAL POLYMORPHISM AND GENETICAL HETEROGENEITY OF COLON CANCER (CC)

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For the past years the role of heredity in predisposition to the CC and its clinical polymorphism were studied using the clinico genetic, immunologic and immunogenetic methods. The base date was formed of 1926 patients with different clinico-anatomical variants of CC that was characterized by the strong clinical polymorphism in period of disease manifestation, phenotype particularities, grade of immunodeficiency etc. The clinical forms of the CC are characterized of the specific proportion in genotypic and environmental predisposition components, which depend on pathway distinctions. The contribution of the heredity in predisposition to the different clinical variants of CC fluctuates from 43% to 92% and correlation coefficients among them are 0.7; 0.87; 0.99. We suppose to clear up the matter of CC independent nosologies availability after special molecular-genetical investigations, which we are realizing now.

707 POSTER

PROGNOSTIC VALUE AND PREDICTIVE FACTORS OF TUMOR STERILIZATION AFTER PREOPERATIVE RADIOTHERAPY FOR RECTAL CANCER

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Between 07/1977 and 10/1993, 147 patients (pts) received preoperative radiotherapy (RT) for rectal adenocarcinoma. There was 64 T2, 56 T3, 25 T4 tumors and 2 relapses after prior surgery. Median total dose of RT was 44 Gy (5–73 Gy), median fractionation 5 fractions (1–5) of 2 Gy (1.5–5 Gy) per week, and median duration of RT 5 weeks (1 day–9