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

weeks). Seventy-nine pts were treated with a 2-field technique, 66 pts with a 4-field technique and 2 pts with a direct perineal field. Median treated volume was 4.4 liters (1.2–9.4). One hundred and twenty pts were treated with X25 MV, the other 27 pts with 1.25 Mev ^{60}Co. All irradiated rectal tumors have been reanalyzed by the same pathologist in order to quantify tumor sterilization. Three groups were individualized according to the residual tumor cell density (RTCD): absence or low, intermediate and high.

All pts underwent surgery in a median delay of 4 weeks. Fifty-five tumors (37%) showed no (9/147) or low (46/147) RTCD; 51 (35%) showed an intermediate RTCD and 39 (27%) a high RTCD. The distribution of the pts according to age, tumor stage, tumor location, delay before surgery and RT parameters (total dose, fractionation, duration of treatment, 2 or 4-field technique, treated volume, X25 MV or 1.25 Mev ^{60}Co photons) was not statistically different in the 3 groups. Five-year actuarial survival rates were 100% in the group of pts with no RTCD, 54% in the group with low RTCD, 44% in the group with intermediate RTCD and 53% in the group with high RTCD. The difference did not reach significance, probably because of the small number of sterilized tumors. These results suggest however that tumor sterilization is a favorable prognostic factor after preoperative RT in rectal cancer.

708 POSTER

IL-8 INVOLVEMENT IN IMMUNE DISREGULATION OF CANCER PATIENTS

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The mechanisms for the recruitment of immune cells to sites of inflammation have not been fully elucidated. In order to understand the mechanisms of IL-8 a potent chemotactic and activating chemokine, during immune response, we examined in colon cancer patients and controls, serum levels of IL-8, IL7, IL-6, IL-4, TNF-α, IFN-γ IL-2, sIL-2R: IL-8 production in supernatants of PBMC with and without activation agents: PBMC phenotype (CD3, CD4, CD8, CD16, CD56, CD57, CD25): PBMC proliferative responses to IL-2, IL-4, anti-CD3. Our results show that IL-8 serum levels in patients (p) were higher than in controls (c) (n.p = 65, n.c = 51 $P = 0.007$) and this was significant only at stage II (n.p = 25 n.c = 51 $P = 0.01$) and III (n.p = 8 n.c = 51 $P = 0.03$). It is of great interest to note that our preliminary data of IL-8 production from: PBMC (n.p = 14 n.c = 4 $P = 0.0002$), plus PHA (n.p = 15 n.c. = 3 $P = 0.008$), plus anti-CD3 (n.p = 3 n.c = 3 $P = 0.03$) show that levels in patients are significantly lower than in controls. Correlation between IL-8 serum levels and other serum cyokines evidenced no significant values, but at stage I (n.p = 9 $P < 0.00001$), II (n.p = 23 $P < 0.00001$) and IV (n.p = 5 $P < 0.00001$) correlations with TNF-α levels were found. The phenotypic analysis showed only a positive correlation between IL-8 serum levels and CD8 expression (n.p = 34 $P = 0.01$). PBMC proliferative responses of patients showed no significant correlations with all examined agents. Analysing our data, it seems that in cancer patients there is a disregulation in IL-8 production. It is to note that in the serum, in this situation are involved the stage II and III, where principally are regulated the mechanisms for lymphonodal infiltration and host invasion. In this contest, the positive correlation between IL-8 and CD8 expression can be interesting information. So, our results support the hypothesis that IL-8 can be an active participant in the disregulation of immune response which allows the tumor to locate and progress in the host.

709 POSTER

COLON CANCER: SIL-2R AND CORRELATED MECHANISMS

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The current research has still not clarified why serum levels of sIL-2R increase in cancer patients. In order to establish whether this could be an independent event or there are correlated mechanisms, in colon cancer patients and controls we examined the level of this soluble receptor in correlation with phenotype of PBMC; serum levels of IL-6, TNF-α, IL-4, IFN-γ, IL-2; changes of HLA-I and HLAII antigen expression on tumor tissue respect to normal mucosa; PBMC proliferative response to IL-2, IL-4, anti-CD3. Correlations with the disease progression were evaluated. Our results show that sIL-2R level of patients (p) was higher than in controls (c) (n.p = 72, n.c = 79 $P < 0.0001$). There were no significant correlations between sIL-2R and the expression of CD3, CD4, CD8, CD16, CD56, CD57, CD25 antigens on PBMC of both patients and controls. In patients compared to controls, even if the serum levels showed an increase of IL-6 (n.p = 56, n.c = 49 $P = 0.0001$), IFN-γ (n.p = 73, n.c = 43 $P = 0.003$), IL-4 (n.p = 24, n.c = 33 $P < 0.0001$) and a decrease of IL-2 (n.p = 42, n.c = 27 $P < 0.0001$), sIL-2R level showed only a positive correlation with IL-4 (n.p = 19 $P = 0.033$). Moreover, from the evaluation of HLA antigens it is possible to note that when the expression of HLAI is the same in tumor tissue and normal mucosa (situation more often present at stage I: 66.7%), sIL-2R of patients was higher than controls ($P = 0.018$). With regard to the correlations with the proliferative response, merely a positive association with IL-2 plus anti-CD3 was determined (n.p = 29 $P = 0.013$). So, from our overall results, as IL-4 is produced by CD4$^+$TH2 cells and the anti-CD3 addition to IL-2 is well-known to be discriminant for the activation of these cells, it seems that the increase of sIL-2R in serum of cancer patients is an event dependent on CD4$^+$TH2 cells. This hypothesis is confirmed by the fact that when HLAI antigen expression was lower than normal, the HLAII antigens was higher, supporting an inflammatory situation.

710 POSTER

CANCER ESTABLISHMENT AND PROGRESSION

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Immunological evaluations on cancer patients provide informations to understand the disregulations which allow the tumor to locate and progress in the host. In colon cancer patients and controls we examined the serum levels of various cytokines and the proliferative response of PBMC to IL-2, IL-4, anti-CD3mAb. Our results show that in patients there was a significant serum increase of IFNγ, IL-4, IL-6, whereas IL-2 significantly decreases. This situation is indicative for the functional presence of inflammatory CD4$^+$TH2 cells. In patients it is possible to note a negative correlation between the proliferative response to IL-2 and stage of the disease ($^*P = 0.0024$), which changes into positive when anti-CD3 is added ($^*P = 0.007$) (indicative for a functional increase of CD4$^+$TH2 cells with the disease progression). Moreover in patients the proliferative response to IL-2 + anti-CD3 was comparable to controls ($\S P = 0.42$), whereas in the former there was a significant reduction after IL-4 addition ($\S P = 0.005$). This effect of IL-4 on IL-2 + anti-CD3 starts at stage II, whereas at stage I the response is still comparable to controls and there is a greater response to IL-2 alone ($\S P = 0.0035$). Analysing our data, it seems that the start of the immunological response in patients is of inflammatory type and it degenerates because IL-4, which raises with the disease progression, interferes with IL-2 mechanisms.

Serum levels	patients compared to controls				*stage correlations	
§ IFN-γ	n = 73	P = 0.003	n = 43	n = 63	r = 0.19	P = 0.14
§ IL-4	n = 24	P < 0.0001	n = 33	n = 24	r = 0.89	P < 0.0001
° IL-6	n = 56	P = 0.0001	n = 33	n = 55	r = 0.21	P = 0.12
° TNFα	n = 56	P = 0.1	n = 33	n = 51	r = 0.35	P = 0.014
§ IL-2	n = 42	P < 0.0001	n = 27	n = 41	r = −0.56	P = 0.0004

*Spearman rank correlations; §Student's t-test; °Mann-Whitney test

711 POSTER

INTRAHEPATIC CHEMOTHERAPY WITH FLOXURIDINE (FUDR) L-LEUCOVORIN (LV), DESAMETAZONE (D) IN CONTINUOUS INFUSION AND BOLUS MYTOMICIN C (MMC) IN HEPATIC METASTASES FROM COLORECTAL CANCER: A PHASE II STUDY

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Intrahepatic continuous infusion FUDR induces 50% response rate (RR) in patients (pts) with hepatic metastases from colorectal cancer (CRC). Lower RR are observed in pretreated pts. The combination of FUDR + LV has given over 70% RR with high hepatic toxicity. The use of D can decrease the hepatic toxicity. In a randomized study Kemeny *et al.* have observed an increase in RR and a decrease in hepatic toxicity in the group of pts treated with FUDR + D compared to the group receiving FUDR only. Moreover the combination of MMC, Carmustine and FUDR is effective also in pretreated pts. On these premises since July 1993 we have treated 22 pts affected by unresectable hepatic