

721

POSTER

HYDROXYUREA (HU), HIGH DOSE FOLINIC ACID (L-FA) AND 5FU VS HU, 5FU AND INTERFERON- α (IFN) IN ADVANCED COLORECTAL CANCER (ACRC): A RANDOMIZED TRIAL OF THE ITALIAN ONCOLOGY GROUP FOR CLINICAL RESEARCH (GOIRC)

F. Di Costanzo, A. Sdrobolini, M. Marzola, S. Zironi, A. Contu, F. Pucci, C. Rodinò, E. Corgna, R. Algeri, G. Bisagni, S. Angiona
GOIRC, Centers of Terni, Ferrara, Modena, Perugia, Thiene, Grosseto, Piacenza, Sassari, Reggio-Emilia and Parma, Italy

We previously reported that a combination of HU, FA and 5FU was better than FA + 5FU (RR: 30% vs 22%; ASCO 463, 1992). From January 1992, 237 pts with histological diagnosis of ACRC, with evidence of advanced disease, not previously treated with chemotherapy, were randomized between **arm A: L-FA** (250 mg/m² in a 2 hour IV infusion) and **5FU** (600 mg/m² IV bolus, 1 hour after FA) plus **HU** (3000 mg, day 1, given per os in three administrations, every 8 hrs, 6 hrs after 5FU) or **arm B: FU** (600 mg/m² IV bolus) plus HU as arm A and IFN (3 $\times$ 10 U/m², sc three times a week). On both arms treatment was given weekly for 6 wks followed by a 2 wk rest period. At the time of this analysis, a total of 203 (86%) pts. are evaluable for response: 102 (86%) and 101 (86%) in arms A and B respectively. The analysed patients are comparable for median age (63 vs 63), sex (M:66 vs 61, F: 36 vs 40), PS (100&-80: 89 vs 88; 70-60%: 13 vs 13). Preliminary analysis shows the following results: on **arm A** 28 (28%) CR + PR, 45 (44%) NC, 29 (28%) P and on **arm B** 8 (8%) CR + PR, 41 (41%) NC, 52 (51%) P. Diarrhea, mucositis and vomiting are the most frequent non-haematological side effects in both arms. Two pts died due to severe gastrointestinal toxicity (diarrhea and mucositis) one on each arm.

722

POSTER

MICROVESSEL DENSITY AND P53 OVEREXPRESSION IN COLORECTAL ADENOCARCINOMA

P.B. Vermeulen, L. Roland, V. Mertens, E. Van Marck, E.A. De Bruijn, A.T. Van Oosterom, L.Y. Dirix
Angiogenesis Group (Lab Cancer Res & Clin Onc) Antwerp University (UIA), B-2610 Wilrijk, Belgium

Cancer is an angiogenesis-dependent disease. The degree of this new vessel development is related to clinical outcome in breast carcinoma. Recent experiments suggest that wild-type p53 regulates the production of thrombospondin-1 (Dameron *et al.*, 1994) and of a glioma-derived angiogenesis inhibitor (Van Meir *et al.*, 1994) and that mutant p53 potentiates VEGF expression (Kieser *et al.*, 1994). We have analysed the relationship of p53 overexpression and microvessel density (MVD), as a measure of angiogenesis, in colorectal adenocarcinoma.

Sections of 42 paraffin-embedded tumours were stained for CD31 (Dako) to detect endothelial cells and for p53-protein-overexpression, both wild and mutant forms, with DO7 (Biogenex).

The majority (76%) of the p53-positive tumours was highly vascular (>90 vessel/ $\times$ 200 field in the areas of intense neovascularisation), with a mean MVD of 114 $\pm$ 43, as compared to only 31% (χ^2 , 7.7, P < 0.05) of the p53-negative tumours, with a mean MVD of 104 $\pm$ 50.

This is comparable to the results of Gasparini *et al.* (1993) in head-and-neck squamous cell carcinoma and indicates an involvement of the p53 tumour suppressor gene in colorectal adenocarcinoma angiogenesis.

723

POSTER

COMPLICATIONS AFTER PREOPERATIVE RADIO-CHEMOTHERAPY TREATMENT OF RECTAL CANCER

C. Fucini, V. Distante, M. Rontini, A. Manetti, C. Elbetti, A. Valiani, L. Ciommi

Clinica Chirurgica I, 50134 Florence, Italy

Preoperative radio-chemotherapy is currently employed to reduce local recurrences of rectal cancer (RC). We reviewed a consecutive series treated with this modality, in order to evaluate the frequency of complications. 47 patients with localized RC were observed from 1990 to 1994. 19 patients (mean age = 62; T2 = 3, T3 = 14, T4 = 2) received preoperative irradiation (45 Gy in 5 weeks) and chemotherapy (5-FU + Leucovorin, refused by one patient), whereas 28 patients (mean age = 66.5; T1 = 1, T2 = 9, T3 = 17, T4 = 2) were treated by surgery alone. All patients had radical surgery, immediately or after (mean = 5 weeks, range 3-18) preoperative treatment.

Grade 3+ toxicity during preoperative treatment was observed in 8 cases (42.1%), being accounted for skin, blood, bladder, and bowel

toxicity in 6, 2, 2, and 3 cases, respectively. 8 patients had radiotherapy/chemotherapy interrupted for major toxicity. One patient in the preoperative treatment group died (mortality 5.2%) for postoperative pulmonary embolism. Complications of surgery were observed in 31.5% of cases in the preoperative treatment group, and in 21.4% of cases in the immediate surgery group (P = 0.3). Anastomotic dehiscence developed in 15.7% and 7.1% respectively; but none of them required second intervention. No difference was observed between the two groups as far as ileus time or hospitalization time were concerned.

Considering the expected therapeutic benefits of preoperative treatment its side effects were relatively moderate and clinically acceptable.

724

POSTER

GROWTH AND DIFFERENTIATION OF HUMAN CACO-2 ENTEROCYTES AFTER TRANSFER OF THE SV40LT ONCOGENE: STATUS OF P53 AND RB

S. Djelloul, M.E. Forgue-Lafitte, M. Mareel², B. Hermelin¹, E. Chastre, C. Gespach

INSERM U55

¹ Service de Biochimie B, Hôpital Saint-Antoine, 75571 Paris 12, France

² University Hospital, Ghent, Belgium

Our previous investigations clearly indicate that the transfer of SV40LT in human and murine intestinal epithelial cells induced alterations of the ultrastructural organization and polarization of the resulting immortalized cell lines. We now demonstrate that the functional expression of the SV40LT oncogene in Caco-2 cells (C2) did not modify the enterocytic phenotype, including expression of villin, sucrase-isomaltase, brush border and dome formation. As compared to C2 cells, the transfected C2LT9 cells exhibited similar growth curves and no change in invasive properties *in vitro*, reduced latency times necessary for manifestation of the tumors *in vivo*, and increased proportion of cells in the S phase of the cell cycle. The LT antigen-RB complexes are clearly identified at the different phases of the growth curve. Differentiation is characterized by the conversion of Rb into hypophosphorylated forms in mature enterocytes.

These results suggest that: (1) C2 cells and Rb exert a dominant control against LT; (2) the enterocytic differentiation is compatible with LT expression when this oncogene is introduced in proliferating cells already engaged in the differentiation process; (3) Rb and its partners may contribute to the genetic and molecular alterations observed during the progression of human colorectal cancer; (4) LT requires p53 for the expression of his oncogenic activity.

725

POSTER

PULMONARY METASTASES (PM) FROM COLORECTAL CANCER (CRC) TREATED BY SURGICAL RESECTION. PROGNOSTIC FACTOR ANALYSIS

M. Ducreux, Ph. Girard¹, P. Baldeyrou¹, Ph. Rougier, Th. Le Chevallier, P. Ruffié, D. Grünewald¹

Institut Gustave-Roussy, Rue Camille Desmoulins, 94805 Villejuif, France

¹ Centre Médico-Chirurgical de la Porte de Choisy, 75013 Paris

To select pts who will benefit from resection we conducted a retrospective prognostic factor analysis on pts with PM from CRC treated by surgical resection between 1970 and 1992. **Population:** 86 pts have been analyzed; median age: 59 years; primary tumor: colon = 49, rectum = 37. 13 pts had prior resection of liver M and 12 received chemotherapy prior to resection of PM. The total number of intervention was 102 (bilateral = 21). Resection was incomplete in 10 pts. The surgical procedure was a wedge resection in 63% of the cases, a lobectomy in 16%, a segmentectomy in 14%, and a pneumonectomy in 5%. No postoperative death occurred. **Results:** overall survival was 24% at 5 years and 20% at 10 years. Prognostic factors of a better survival determined using univariate analysis were: a CEA level lower than 5 ng/ml (P = 0.0001), a complete resection (P = 0.00001) and less than two metastases (P = 0.03). Localization of the primary tumor, prior resection of liver metastases, size of the PM and time elapsed between the diagnosis and the resection of the PM did not influence survival. Using multivariate analysis, a low CEA level and a complete resection remained independent predictive factors (P = 0.0001, P = 0.03, respectively). **Conclusion:** Surgical resection of PM allows long term survival especially for pts with a normal CEA level prior to surgery. The number of preoperative PM does not appear to be a limiting factor when lesions are totally resectable.