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PROGRESSION OF FAP-DERIVED HUMAN COLONIC CELLS AFTER TRANSFER OF THE SRC ONCOGENE ALONE OR COMBINED WITH THE POLYOMA EARLY REGION. INTERACTION WITH THE MET/HGF SYSTEM

S. Empereur, E. Chastre, Y. Digioia, P. Dalla Zonca[1], M. Mareel[2], C. Paraskeva[3], C. Gespach
INSERM U55, Hôpital Saint-Antoine, 75571 Paris 12, France
[1]University of Torino, Italy
[2]University Hospital, Ghent, Belgium
[3]University of Bristol, U.K.

Functional insertion of activated src or PyMT oncogenes induced the tumorigenic potential of PC AA/C1 cells in athymic mice. Transfer of the Py early region genes alone or combined with c-src shortened the latency period and induced highly progressive tumors. PC cells transfected by mutated src induced exhibited elevated $pp60^{src}$ tyrosine kinase activity, HGF-dependent invasion in collagen gels and overexpression of MET by Northern and Western blots. Expression of the HGF gene was detected by RT-PCR and Southern blot in parental and oncogene-transfected cells.

Our results indicate that activation of the src tyrosine kinase, an early event during human colon cancer progression, may be involved: (1) in the adenoma-carcinoma conversion, (2) activation of the invasion and metastatic cascades under the control of HGF and MET.

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A PHASE II STUDY OF CPT 11 (IRINOTECAN) IN REFRACTORY TO 5 FU COLORECTAL CANCER (CRC) WITH, PREVENTIVE TREATMENT OF DELAYED DIARRHEA BY ACETORPHAN

J.M. Extra[1], Ph. Rougier[2], M. Ychou[3], J.Y. Douillard[4], A. Adenis[5], M. Mousseau[6], S. Assadourian[7], M. Mahjoubi[7], M. Marty[1]
[1]Hôpital St Louis, Paris, France
[2]Institut Gustave-Roussy, Villejuif, France
[3]Centre Val d'Aurelle, Montpellier, France
[4]Centre René Gauducheau, Nantes, France
[5]Centre Oscar Lambret, Lille, France
[6]CHU Grenoble, La Tronche, France
[7]Bellon, Neuilly S/Seine, France

According to Phase I data, Acetorphan a new anti-secretory anti-diarrheal agent might reduce the incidence and severity of CPT 11 induced diarrhea. In an attempt to confirm these results, an open randomized study has been performed, using this specific enkephalinase-inhibitor: Acetorphan (A). All patients (pts) had advanced CRC refractory to 5 FU and were treated with CPT 11 at the dose of 350 mg/m^2 every 3 weeks.

In this study, the role of prophylactic A, 100 mg × 3/d has been randomly assessed versus no prophylaxis. Eighty eight pts have been so far entered and 45 are evaluable. Preliminary results suggest no difference in term of incidence or severity of D, but a trend towards a shorter duration and later occurrence of D in cycle 1 (3 versus 4.5 days and day 6 versus day 5 respectively) in patients receiving A and surprisingly a decrease in the incidence of grade 3 + 4 (OMS) neutropenia and febrile neutropenia.

Conclusion. The new anti-diarrheal agent A, may be of interest in the prophylactically management of CPT 11 induced diarrhea. Final results of these studies will be presented.

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EXPRESSION OF ADHESION MOLECULES RELATED TO TUMOUR-PROGRESSION IN COLORECTAL CARCINOMA: GRADING, STAGING AND FOLLOW UP

L.H. Finke, H.J. Terpe, T. Gerneth, C. Zörb, P.M. Schlag
UKRV Robert-Roessle-Klinik am Max-Delbrueck-Centrum für Molekulare Medizin, Abtl. für Chirurgie und Chirurgische Onkologie, D-13122 Berlin, Germany

Introduction: Tumour progression and metastasis is accompanied by altered expression of adhesion molecules. The purpose of this prospective study was to analyse expression of adhesion molecules in colorectal carcinomas based on a cohort derived from a single surgical oncology center. At that end CD44 variant isoforms, E-Cadherin, β-Catenin as well as α- and β-integrin subunits were investigated both on the mRNA- and on the protein level. Snap frozen samples of normal colorectal mucosa, primary tumours, and metastases were collected from 120 patients during 1992–1994. All data were correlated to TNM-stages and clinical status. *Results:* CD44H is broadly expressed in all tissues. CD44 variant isoform expression is transient, being up-regulated as early as in adenomas. Maximum expression is observed in UICC stage III primary tumours, but significant loss of CD44 isoform expression is observed in all sites of metastasis. Adherent junction molecule expression is correlating with histological grading. The same is observed for α-2,3,6- and β-1,3,4-Integrins. *Conclusions:* The strength of expression of various molecules in CRC tissue specimens is correlating with histological grading. Up-regulation of expression during tumour suppression is very rare, while down-regulation accompanying increased de-differentiation is the predominant scheme. Only a few molecules studied in this work match valuable prognostic parameters such as TNM-staging or even survival. These could therefore beneficially contribute to the evaluation of the individual tumour patient's prognosis.

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HIGH DOSE 5FU BIOMODULATION BY HIGH DOSE LEUCOVORIN AND INDIVIDUAL 5FU DOSE ADJUSTMENT IN METASTATIC COLORECTAL CANCER. A MULTICENTRIC PROSPECTIVE STUDY OF 130 PATIENTS

E. Gamelin, R. Delva, Y. Dumasnil, J. Jacob, Ph. Maillart, M. Boisdron Calle, M.-J. Goudier, A. Lortholary, A. Hardouin, J. Geslin, J. Hetroy, F. Larra
Etude multicentrique, Pays de Loire-Bretagne-Poitou, Centre Paul Papin, 2 rue Moll, 49033 Angers Cedex 01, France

Extrahematopoietic toxic side effects limit 5FU dose intensification. In a previous study with 5FU dose escalation, a pharmacokinetic follow up led us to define a therapeutic index. 5FU plasma level range: 2.5 to 3.5 mg/l (AUC: 20 to 28 mgxh/l (Proc. AACR 92). *Study:* a phase II prospective study was carried out from 05/1991 to 12/1992. Weekly 8 hour infusion high dose 5FU were potentiated by 400 mg/m^2 leucovorin. The initial dose of 5FU, 1300 mg/m^2, was adapted weekly, according to a 5FU plasma levels follow up (HPLC) to obtain the optimal therapeutic range previously determined. The therapeutic efficiency was evaluated after 2 months in the optimal range. *Results:* 130 patients (pts); no prior chemotherapy or only adjuvant chemotherapy (18 pts); mean age 62 (27–75); initial P.S.: 0 (28%); 1 (26%); 2 (36%); 3 (3%). *Metastatic sites:* liver (71%); lung (20%); lymphnodes (8%); other (11%); local recurrence (17%); measurable disease (89%). **Toxicity for the whole treatment** (mean: 9 months (mo); diarrhea (39%) (4 grade III); handfoot syndrome (30%) (4 grade III); mucositis (4%); W.H.O. grade toxicity: I (22%); II (25%); III (3%); IV (0%). *P.S. after 2 months:* improved for 50% pts. *Response rates:* CR (17%); PR (39%); minor + stable disease (29%); progression (15%); mean duration of response (15.5 mo). *Overall survival and disease free survival:* at 1 year (68.5%, 53%); at 2 years (38%, 18%); median survival: 15 mo; mean disease free survival: 11 mo. *Pharmacokinetics Study:* 5FU dose necessary to obtain therapeutic levels: at 3 months (3 g, s.e. 68, 0.9 g to 4.5 g), at 6 mo (3.5 g, s.e. 450, 1 g to 7 g). Five pts were immediately in a highly toxic zone. Time necessary to obtain the therapeutic levels was predictive for the quality of the response (CRvsPR + ST: 3 vs 6 courses). Variations of 5FU metabolism were observed during the treatment leading to a 5FU plasma levels decrease or increase. They required a 5FU dose adjustment to maintain the optimal 5FU levels to prevent tumor escape or acute toxicity. *Discussion:* we have started a multicenter phase III trial comparing a constant dose of 5FU and an individual 5FU dose adjustment to prove the benefit of a pharmacokinetics follow up.

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PRE-OPERATIVE RADIOTHERAPY TO PREVENT LOCO-REGIONAL RECURRENCE IN RECTAL CARCINOMA

J.P. Gerard, D. Fric, R. Coquard, L. Ayzac
Service de radiothérapie CHU Lyon Sud, 69495 Pierre Benite Cedex, France

Aim of study: To analyze local control rate and survival of a series of patients included in a phase I–II pilot study.

—Patients and treatment: Between 1980–92, 170 patients were included. Median age: 61 Y, sex ratio: 1.7 M/F. All patients with proven adenocarcinoma (7% poorly differentiated) of the rectum. Clinical stage: T2: 68, T3: 85, T4: 17. After irradiation and surgery pathological staging was: pT0: 24, pT1: 22, pT2: 43, pT3: 73, pT4: 8, pN0: 128, pN1: 42.

Radiotherapy (RX) was given with a patient in the prone position. 3 fields technique 18 MV × rays. Accelerated schedule: 39 Gy/13F/17 days. Surgery performed between 1 to 9 weeks after the end of RX. No chemotherapy.