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POSSIBLE ROLE OF THYMIDYLATE SYNTHASE LEVEL IN HUMAN COLO RECTAL CARCINOMA: A NEW PROGNOSTIC FACTOR?

R. Sanguedolce°, C. Flandina°, V. Bazan°°, A. Grassadonia°, G. Modica°°, A. Russo°° and L. Rausa°.
°Inst. of Pharmacology, °°Inst. of Clin. and Phys. Surgery, C.I.R.O.C., Policlinico "P. Giaccone", Palermo, Italy.

The Thymidilate Synthase (TS) level has been examined in human colorectal carcinomas (CRCs) and in normal colorectal mucosa to evaluate the possibility to consider TS a prog nostic factor of disease and to correlate enzyme levels to the time of progression of disease. The enzyme levels have been determined in 58 pts with operable CRC, untreated with previous chemotherapy. The follow up for pts lasted at least 30 months. Only 32 of these pts were eligible for this study. In 7 out of these 32 pts we performed the TS deter mination in segments of normal mucosa, after histological control (0.003 pmol/mg protein and 0.060 pmol/mg protein in CRCs). It is worth noting that the time to progression of disease has been longer for those pts who had a TS higher level (0.075 pmol/mg protein, n=18, P<0.01). There is no correlation with grading, staging, sex and age of pts. We will complete this study with determination of ploidy and S phase. Supported by A.I.R.C., Milan, Italy.

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5-FLUOROURACIL (FU) and FOLINIC ACID (FA) plus beta - INTERFERON (b-IFN) for TREATMENT of METASTATIC COLO-RECTAL CANCER.

L.Pavesi [1], G.Attardo [2], G.Fiore [3], P.Gallotti [4], P.Cardellini [5], B.Massidda [6] and G.Robustelli della Cuna [1].

Division of Medial Oncology, Clinica del Lavoro Foundation -Pavia [1], Divisions of Internal Medicine of: Mede [2], Novi Ligure [3], Vigevano [4], and Voghera [5], Medical Oncology, University of Cagliari [6] - Italy.

From February 1991 to December 1992 , 67 patients (pts.) with histologically proven metastatic colorectal cancer (colon 35 , rectosigmoid 32 pts.) were treated in an outpatient setting with FA (100 mg /m^2 bolus iv.) followed by 15 ' infusion of FU (375 mg/m^2) for 5 consecutive days , q.3 weeks until progression , refulsal or severe toxicity . b-IFN (3 x 10^6 UI) was administered im. during chemotherapy and three times a week in the intervals between chemotherapy. Pre-treatment characteristics of evaluable pts. were : median age 60 yrs. (40-70) , M/F 32/28, median K.B. 80 (60-100) , previous adjuvant therapy 9.6% (chemotherapy 4 and radiotherapy 2 pts.) ; 59 pts. (95.1 %) did not receive any treatment for metastatic disease. Dominant metastatic sites were : liver 72% , lung 6%, bone 3.3% , intra-abdominal nodes 8%. A total of 408 courses was administered and the median number of cycles per pts. was 6 (range 3 to 12). In 62 evaluable pts. (not evaluable : 3 lost after the 1st cycle, 2 early deaths) , 6 CR and 17 PR > 50% were achieved : overall response rate 37% (95% C.I.= 25 - 49%). CRs +PRs were 16/31 (51.6% - 95% C.I.= 34.6 - 68.6%) in colon cancer as compared to 7/31 (22.5% - 95% C.I.= 7.8 - 37.2%) in rectosigmoid cancer (p=.02) . Intra-abdominal nodes (3/6 = 50%) and visceral (20/45 = 44.4%) were the most responsive metastatic sites . Overall median duration of response was 7 mos. (CR = 9 mos., PR = 5.5 mos.). Disease stabilization (SD) was recorded in 25 pts. (40%) with a median duration of 6 months, while 13 pts. (20%) experienced disease progression (P). No additonal toxicity was recorded with the use of b-IFN : leukopenia (15%), thrombocytopenia (2%) , nausea and vomiting (12%), oral mucositis (10%) and diarrhoea (14%) were the most important treatment-related adverse events. The low grade intensity of such events never required treatment delay or interruption. The modulation of FU with folinic acid and b-IFN is an effective and well tolerated treatment for metastatic colon cancer . In planning future trials one may consider the observed statistical difference in response rate between colon and rectosigmoid tumors.

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TREATMENT OF METASTATIC COLORECTAL CANCER. A RANDOMIZED TRIAL COMPARING 5FU, 5FU AND MMC AND FTORAFOUR p.o. AND MMC.

H. Hayat, T. Tichler, H. Brenner

Oncology Center, Sheba Medical Center, Tel Hashomer, Israel.

The aim of this study was to evaluate the response rate of Ftorafour and Mitomycine C in patients with metastatic colorectal cancer compared to 5FU and Mitomycine C and 5FU alone. 100 patients were randomized to receive as an initial treatment: 1) 5FU alone 15mg/kg every week (Group A). 2) 5FU 15mg/kg every week and MMC 10mg/m2 every 6 weeks. 3) Ftorafour 800mg p.o. every day and MMC 10mg/m2 every 6 weeks. (Group C). These 3 groups were similar in terms of performance status, age, sex, initial stage and site of metastases. The response rate (CR,PR) was 29% in group A, 25% in group B (CR,PR) and 18% (PR only) in group C. Difference in survival was found at one year in group A and B vs group C (56%,54%,20%) but not at 2 years. Toxicity was mild in the 3 groups. MMC did not add to response rate or survival. Ftorafour p.o. was well tolerated but at this dose was not effective.

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NEOVASCULARIZATION IN HUMAN COLORECTAL ADENOCARCINOMA: A PROSPECTIVE AND COMPARATIVE STUDY

P.B. Vermeulen, L.Y. Dirix, D. Verhoeven, E. Van Marck, D. Van Bockstaele, E.A. De Bruijn, A.T. Van Oosterom - Departments of Oncology, Pathology and Hematology, University Hospital, Antwerp, Belgium

New vessel development is of crucial importance for tumorgrowth, spread of tumorcells via the bloodstream and the growth of metastases. The amount of neovascularization measured in histological sections of breast carcinoma correlates with the occurence of metastasis (Weidner et al., NEJM 1991).

In this study quantification of angiogenesis in human colorectal adenocarcinoma is done by comparing light microscopy, with and without the aid of computerized image analysis, with flow cytometry. For histomorphometrical assessment of vessel density the endothelial cells are stained for factor VIII, with Ulex Europaeus and with CD34, CD31 and CD36 monoclonal antibodies (Horak et al., The Lancet, 1992). For flow cytometry, these monoclonal antibodies label the endothelial cells within the single cell suspension, resulting from mechanical and enzymatical disaggregation of a fresh tumor specimen. Tumorneovascularization is measured by counting the labeled cells, showing a mean of 3.0 % (SEM:1.2%) CD31 and 0.96 % (SEM:0.35%) CD34 labeled cells (n=5).

Investigation of the onset of neovascularization in the colorectal epithelial system is done by comparing vessel density as well as qualitative properties in precancerous polyps, carcinoma in situ and different stages of invasive cancer. Quantification of tumor angiogenesis will be compared with other parameters as a possible independent predictor of prognosis. An update of our results will be presented.

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DOSE-INTENSIFICATION OF MITOMYCIN (MMC), METHOTREXATE (MTX), MITOXANTRONE (NOV) (3 M regimen) WITH G-GSF RESCUE AS FIRST LINE THERAPY OF METASTATIC BREAST CANCER.

P.Pedrazzoli [1], A.Martoni [2], P.Preti [1],.C.Zamagni [2], G.A.Da Prada [1], G.M. Capotorto[3], L.Pavesi [1], G.Poggi [1], F.Pannuti [2], and G.Robustelli della Cuna [1].
Divisions of Medical Oncology: Clinical del Lavoro Foundation - Pavia[1], Ospedale S.Orsola - Malpighi - Bologna [2], Casa Sollievo della Sofferenza , S.Giovanni Rotondo [3] - Italy.

3 M regimen has been reported as an effective treatment of advanced breast cancer (ABC) with approximately 50% objective response , leukopenia being the major dose - limiting side - effect (Powles J.T. et al.,Excerpta Medica ,1987). Furthermore a clear cut relationship does exist between dose-intensity and clinical outcome in ABC (Hryniuk W.M.,JCO,1984). With the aim to ascertain the feasibility and tolerability , as well as therapeutic efficacy of intensified 3 M regimen, we shortened the drugs administration intervals as follows : MMC : 7 mg/m2 every 4 weeks, MTX : 35 mg/m2 and NOV : 7 mg/m2 every 2 weeks, all drugs being administered iv. bolus injection on day 1 for a total of 6 projected courses. Recombinant human G-CSF (5 µg / kg/day) was given subcutaneously from day 2 to 12 after each course. Treatment was repeated if absolute neutrophil counts were > 1.5 x 109/ l and platelet counts > 100 x 109 / l. Between Dec.1991 and Jan .1993 , 30 patients (pts.) with histologically proven and progressive ABC , previously untreated with cytotoxic chemotherapy for advanced disease, were enrolled by partecipating Institutions. The main pts. characteristics were : median age 53 yrs. (28-71), premenopause 18 , postmenopause 12 , disease free- interval 34 months (0-132), metastatic sites: bone 9 , skin 11 , nodes 10 , lung 11 , liver 9. At Jan.31,1993 a total of 144 courses were administered: 24 pts. completed the planned 6 courses , 3 were still being treated , 3 pts. did not complete treatment (1 refusal , 2 early death for progressive disease). Objective response was recorded in 15 pts.(2 CR and 13 PR >50%) for an overall reponse rate of 65 % (95% C.I. = 46-84%). Median duration of response was 4+ months (4 - 11+ months). Chemotherapy- related toxicity was mild (WHO : G1- 2 mucositis , nausea and vomiting) . G-CSF - related side - effects were transient and mild bone pain (4 pts.) and rash (2 pts.). Hematological rescue has been achieved in nearly all treated pts. ; only 3 courses had to be postponed due to myelotoxicity : two for thombocytopenia (platelet counts 69 x 109/l and 41 x 109/l respectively) , one for neutropenia (neutrophils count 1.0 x 10^9/l). Our results support the following conclusions : a) shortened 3 M regimen with G-CSF rescue is feasible for at least 6 courses and well tolerated ; b) this schedule allows dose-intensification over standard 3M combination by reducing time intervals of drug admiminstration ; c) response rate observed are encouraging and deserve futher investigation on a larger number of patients.

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PHASE II STUDY WITH TOPOTECAN IN COLORECTAL CANCER Verweij J., Wanders J., Calabresi F., Franklin H. and Kaye S.B. for the EORTC Early Clinical Trials Group.
Rotterdam Cancer Institute, PO Box 5201, 3008 AE, Rotterdam, The Netherlands.

Topotecan (SK&F 104864-A, NSC 609699) is a semisynthetic camptothecin analog. Topotecan was active in tumor models such as L1210, P388, HT-29, B16, M5076 and Lewis lung. The drug acts through specific inhibition of topoisomerase 1. In phase I studies activity was mainly seen with daily times five regimens. For this reason this regimen was selected for phase II studies. The dose limiting toxicity was leucocytopenia. The recommended dose for phase II studies was 1.5 mg/m^2/day, giving the drug i.v. over 30 minutes on 5 consecutive days every 3 weeks. We performed a phase II study in patients with colorectal cancer not previously treated with chemotherapy.

Twenty-one patients (pts) entered the study. One was ineligible because of non-measurable lesions, 4 are too early. The remaining were 7 males and 9 females, median age 63 years (range 47-74), median WHO performance score 1 (range 0-2). Metastatic sites were lung (7), liver (11) and miscellaneous (10). Response was evaluated every 2 cycles according to WHO criteria, toxicity was scored according to CTC-criteria. Sixteen pts, 34 courses are presently evaluable for toxicity which mainly consisted of leucocytopenia in 33 courses (97%), being grade 3-4 in 50%, without any septic complication. Thrombocytopenia occurred in 16 courses (47%). Other side effects consisted of nausea and vomiting grade 1-3 in 20 cycles (59%), hypotension grade 1 in 4 cycles (12%) and alopecia grade 1 in 9 pts (56%). One pt achieved a partial response. In addition a 50 % decrease in tumor size lasting less than 4 weeks was seen in 1 pt. Topotecan at this dose and schedule exerts some antitumor activity in colorectal cancer, other schedules may merit further exploration.