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FLUOROURACIL, FOLINIC ACID AND INTERFERON ALPHA OR FLUOROURACIL AND FOLINIC ACID ALONE IN AMBULATORY PALLIATIVE TREATMENT OF METASTATIC COLORECTAL CANCER

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Due to actual developments in treatment strategies since 1990 12 patients (pts) with metastatic colorectal cancer were treated with 5-Fluorouracil (5-FU), folinic acid (FA) and Interferon 2b (IFN) (group A). Since 1991 13 pts were treated with high dose 5-FU and FA alone (group B). All pts were accepted at first signs of progression and were treated 4-5 months; additional therapies were performed in reoccurence of progress. Group A: All pts were given weekly regiments of IFN 3 x 5 mio U sc; 8 pts (group A1) received an induction therapy of 200 mg/sqm FA (15 min) followed by 400 mg/sqm 5-FU (4 h) intravenously during the first 6 days and then subsequently weekly ambulatory maintenance treatment at the same concentrations. Once a week 4 pts (group A2) received 200 mg/sqm FA (15 min) followed by high doses 2g/sqm 5-FU (24 h) 3 x 6 weekly cycles. Group B: No patient received IFN. 13 pts were given FA and high doses 5-FU as described above (group A2). Results: Group A: 12 ts: 1 complete remission (CR) group A1; 2 partial remissions (PR) 1xA1, 1xA2; 5 stable diseases (SD) 3xA1, 2xA2 and 4 progressive diseases (PD) 3xA1, 1xA2. Group B: 13 pts: 1 x CR, 4 x PR, 6 x NC, 2 x decreasing tumor markers in the second treatment cycle prior to staging. Side effects: Group A: Acceptable well known side effects mainly due to IFN treatment (WHO 1-2). Group B: Mainly minimal side effects (WHO 1) due to nausea 24 h post treatment. Conclusions: This high dose 5-FU-regiment seems to be highly active in metastatic colorectal cancer. With respect to side effects 5-FU and FA treatment is less toxic in comparison to additional IFN therapy and therefore better accepted by the patients.

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PHASE II STUDY OF FOTEMUSTINE-5 FU-LEDERFOLINE (FU-FOL) IN METASTATIC COLORECTAL CARCINOMAS (CRC) : PRELIMINARY RESULTS.

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FU-FOL is the reference protocol in metastatic CRC but yields only 16 to 45 % response rates with a 12 month median survival. To improve these results, other efficient drugs must be studied. As a single agent, FOTEMUSTINE had poor results but pre-clinical studies showed a synergystic activity between Fotemustine and FU-FOL on colon cell lines (Fischel CCP, 1991). Therefore, a first line therapy using this combination was studied in 10 patients (pts) (8 M, 2 F) with median age = 60 years (33-69). All pts had histologically proven CRC with metastases in the liver (n=7), lung (n=3),or other sites (n=2). WHO performant status ranged between 0 and 2. Protocol : D1 = FOTEMUSTINE = 100 mg/m² in a one hour perfusion ; D2 to D6 : FOLINIC ACID intravenous (IV) bolus = 20 mg/m²/d before the IV perfusion of 5FU = 370 mg/m²/d, every 4 weeks. Results according to WHO criteria : three of 9 pts had a PR during 13, 41 and 48+ weeks, four had a ST (8, 12, 19 and 23 weeks) and two progressed.One patient received only one course due to persistant thrombopenia and had a minor response. Toxicity was mild with gr III diarrhea n=3, gr II or III vomiting n=5, gr III and IV hematologic toxicity n=2 for WBC, and n=2 for platelets. Conclusion : These preliminary results must be confirmed on a larger scale and by a randomized study versus FU-FOL with regard to survival.

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DOUBLE BIOCHEMICAL MODULATION OF 5-FLUOROURACIL (5FU) WITH METHOTREXATE (MTX) AND LEVO-FOLINIC ACID (LFA) IN THE TREATMENT OF PATIENTS WITH ADVANCED DIGESTIVE MALIGNANCIES.

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From Aug. 1991 to Feb. 1993, 84 consecutive pts affected by advanced digestive malignancies were treated every other week with LFA 250 mg/sqm (2-h iv infusion) followed by 5FU 600 mg/sqm (iv bolus). MTX 250 mg/sqm (2-h iv infusion) was given 24 h before LFA + 5FU. However, preliminary assessment in the first 21 courses detected a median MTX serum concentration of only 0.4 mcM/L at 24 h after its infusion. Therefore, MTX dosage was escalated to 500 mg/sqm in subsequent cycles to reach a median level > 1 mcM/L. Presently, 19 pts are too early to evaluate, and 5 pts received less than 4 courses of therapy because of rapid worsening of clinical status. Among 60 evaluable pts, there were 28 males and 32 females, with a median age of 59 (range, 32-74) years and a median PS of 1 (range, 0-2). Primary was rectum in 20 cases, stomach in 20, colon in 11, gallbladder in 7, and pancreas in 2. 39/60 pts were previously treated, mainly with fluoropyrimidine + LFA. Adequately treated pts received a median number of 8 (range, 4-24) courses of chemotherapy. Four out of 21 (19%) previously untreated pts and 2 out of 39 (5%) previously treated pts achieved a PR, while 25 pts (11 untreated) showed a SD. Responses were observed in all types of treated malignancies with the only exception of advanced rectum carcinoma. Side effects of our therapy were acceptable, since diarrhoea of grade 2-3 was sometimes reported during treatment in 16 (38%) pts only, and hematologic toxicity was quite negligible. Our preliminary data confirm that a double biochemical modulation of 5FU, with MTX given 24 h before and LFA administered concurrently, did not increase the expected toxicity of LFA/5FU combination, and could stabilize also a disease in progression after a previous treatment.

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Combined approach in the conservative management of rectal cancer.

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The management of carcinoma of the middle third and lower rectum usually implies a radical resection . Low anterior resection with stapler has extended sphincter preservation in recent years without compromising cure or local control in comparison with the abdominoperineal operation. Nonetheless, 40-60% of resectable tumors of the lower rectum are usually treated by this latter procedure. For some patients, a permanent colostomy is psychologically unacceptable. Many patients do not benefit from these radical procedures which carry a significant morbidity, especially in the geriatric population.

From 1980 to 1992 we developed a protocol combining preoperative external irradiation (35 Gy in 3 weeks), local excision and peroperative placement of a plastic tube loop for postoperative interstitial irradiation (20 or 25 Gy) with iridium 192, for invasive adenocarcinoma of the middle and lower rectum in 51 patients (median age of 72 years). This is a report of 42 patients with a minimum follow-up of 3 years. Tumors were located in the lower rectum in 32 cases (76%) and in the middle thrid in ten cases (24%). The tumor diameter was less than 3 cm in 3 cases, between 3 cm and 5 cm in 32 cases, and more than 5 cm in 7 cases. Thirty two tumors were well differentiated, eight were poorly differentiated and two were colloid carcinoma. The 3 years NED survival is 83 %. There were 6 local recurrences (14%) and 3 patients developed distant metastatic disease. There were few complications and the patients with local control have normally functionning sphincter.

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LONG-TERM SURVIVAL OF PATIENTS WITH UNRESECTABLE METASTATIC COLORECTAL CANCER TREATED WITH CHRONOTHERAPY.

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From 9/87 to 2/91, 139 patients (pts) with inoperable metastatic (met) colorectal cancer were registered in chronotherapy protocols of circadian-rhythm modulated intravenous delivery of 5-FU with FA and oxaliplatin (L-OHP) or with FUdR into the hepatic artery (iha). All courses lasted 5 days (d) q. 21 d. Respective daily doses (mg/m^2) were : 5-FU, FA and L-OHP i.v. : 700, 300 and 25 ; 5-FU i.v. and FUdR iha: 1200 and 80. Criteria for inoperability were: more than 3 met. in one organ ; more than one organ involved ; resection with curative intent involving > 70 % liver. 40 % pts had more than one met. site, 80 % had liver involvement, 48 % had received previous chemotherapy (32 % were clinically-resistant) and 69 % had W.H.O. performance status 0 or I. Twenty-four pts (17 %) are alive on 2/93 at 42 months' median follow up (24 to 73 mo. from 1st course of chronotherapy). Eleven pts (8 %) have remained disease-free and treatment-free for the past 12 mo. All of them had surgical removal of liver met. following an objective response after chronotherapy. These 24 long-term survivors are : men (N = 14 pts), primary colon (14 pts), well differentiated ca. (9 pts), single organ involvement (17 pts), synchronous met. (17 pts), prior chemotherapy (8 pts), P.S. = 0 (15 pts), median age (58 y.o. ; 41 to 75). Long-term survival or potential cure may be achieved in pts with unresectable metastatic colorectal cancer, through the present agressive chronotherapy-surgery program.

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TOTAL RECTAL RESECTION, COLO-ANAL ANASTOMOSIS AND "J" RESERVOIR IN LOWER THIRD RECTAL CANCER

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A consecutive series of 50 patients (median age 62 years; range 30 - 79), 26 males and 24 females underwent radical rectal resection extended to the dentate line and colic J shaped pouch with handsewn colo-anal anastomosis, from March 1990 to March 1993. A temporary colostomy on the trasversum was associated in all cases and is to be removed in about 2 months.

They were affected by lower third rectal cancer (8 pts. Dukes A; 11 pts. Dukes B; 20 pts. Dukes C; 3 pts. Dukes D; 4 pts. villous adenoma with severe displasia and 4 pts. anastomotic recurrence after Anterior Resection).

The median distance from the lower margin of the tumour to the anal verge was 5.4 cm (range 2,5 - 8 cm) for 46 evaluable patients.

Surgery was followed by chemotherapy (5 FU + Folinic Acid) in 15 pts. (Dukes C/D) and radiotherapy in 29 pts. (Dukes B/C/D).

Only one patient died for MOF after surgical procedure; seventeen patients presented a radiological subclinical fistula and were treated with TPN for two weeks. No patients in our series claimed relevant impairment concerning anal sphincter or urinary functions.

Median hospital postoperative stay was 17 days.

The median follow-up of 14 months (range 1-36) detected seven (14%) local recurrence, but none to the anastomotic site. Two patients with synchronous liver metastases died of progressive disease the first 6 months and the second 10 months after surgery.

The excellent quality of life, good cure rate and lack of major complications suggests that sphincter saving procedures are adequate in treatment of lower third rectal cancer.