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Guest Editors:

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## H20 GEMCITABINE (dFdC), 5-FLUROURACIL (5FU), AND FOLINIC ACID (FA) IN THE TREATMENT OF PATIENTS WITH GASTRO-ENTERIC CARCINOMAS: A CLINICAL AND PHARMACOLOGICAL STUDY.

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5FU and dFdC are two pyrimidine anti-metabolites with know activity in solid tumors. A possible synergic anti tumor interaction between these two drugs has been recently reported We evaluated the effects of dFdC on the anti-tumor activity, pharmacokinetics, and pharmacodynamics of 5FU, in pts with gastroenteric malignancies. FA (100 mg/sqm) and 5FU (400 mg/sqm) were administered IV in a 30 min infusion on the day 1,2,3,4,5 of each cycle. dFdC (1 g/sqm in a 30 min infusion) was given 1 h before FA and 5FU on the day 1, and given again on the day 8 and 16. Cycles were repeated every 28 days Twenty three patients (pts) with pancreas carcinoma, 9 with colo-rectal carcinoma, 4 with biliary tract carcinoma, 1 with gastric carcinoma, 2 with liver metastases by unknown primary site adenocarcinoma completed 3 cycles of chemotherapy and were evaluable for clinical response One complete response (1 colon carcinoma), 9 partial responses (7 pancreas carcinoma, 1 biliary tract, 1 unknown primary site adenocarcinoma), 10 disease stabilizations (8 pancreas carcinoma, 1 colon cancer, 1 unknown primary site adenocarcinoma), and 8 progressions of disease (3 pancreas carcinoma, 3 colon cancer, 2 biliary tract) were recorded. Ten pts were not valuable for response for early exclusion from the study due to the occurrence of side effects (4 pts) and sudden life treathning tumor related complications (8 pts) during the first cycle of treatment Reversible grade I-II gastroenteric and hematological toxicity and asthenia were the most common side effects Reversible grade IV toxicity was reported in 3 pts. Reversible grade II-III- gastroenteric toxicity was reported in 10 patients and reversible haematologic toxicity in 4 pts. In a pharmacokinetic comparison of patients given dFdC plus FA/5FU (N=31) or FA/5FU only (N=16) dFdC enhanced the systemic exposure to 5FU in cancer patients by increasing its AUC, Cmax, and plasma half-life and by reducing its $Cl_T$ and $V_D$ The most active 5FU metabolites were detected in all dFdC plus FA/5FU treated patients and in none of the patients who received FA/5FU alone DFdC dose dependently enhanced the incorporation of 5FU into human activated lymphocytes and a colon carcinoma cell line and significantly increased 5FU cytotoxic metabolites and cytotoxic activity Conclusions Pharmacological and clinical results from this study provide the rationale for using dFdC and FA/5FU in combination for the treatment of pancreas and colon carcinoma. Supported by a grant from MURST (ex-40%)

## H21 THE ROLE OF COLONSCOPY IN FOLLOW-UP AFTER COLORECTAL CANCER SURGERY

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The international literature shows that the intensive follow-up programs for patients operated on for colorectal cancer failed to show any benefit on survival rate. In these studies colonoscopy failed to detect early recurrences. The aim of this study is to evaluate if colonoscopy has any role in an intensive follow-up program, after colorectal cancer surgery.

A total of 348 patients (153 female, 195 male; median age: female 68, male 66) operated on for colorectal cancer at the Department of Surgery, University of Genoa (DICMI) from January 1990 to January 2000 underwent an intensive follow-up program. Our follow-up schedule consisted of clinical and biochemical checks every three months during the first two years and every six months until the fifth year. Pulmonary X-ray and liver ultrasonography were performed every twelve and six months respectively. Colonoscopy and wos performed every two years in 178 patients for a total of 497 examinations.

Local recurrences were found in 10 ( 5,6% ) patients and metachronous carcinomas were detected in 6 ( 3,3% ) patients. Only 2 patients with a local relapse ( 1,1% ) and 4 patients with a metachronous carcinoma were submitted to radical surgery. Adenomatous polyps were detected and removed in 41 ( 23% ) patients.

Our data confirm that the colonoscopy in intensive follow-up schedule failed to improve resecability ratio in local recurrences. Therefore it is our opinion that the primary purpose of surveillance colonoscopy after surgical resection of a colon cancer is to detect metachronous adenomas and not recurrent cancers.

## H22 A PHASE II STUDY WITH 5-FLUOROURACIL (5FU), LEUCOVORIN (LV) AND IRINOTECAN (CPT-11) IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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**Introduction** a phase II trial study was conducted in order to evaluate the activity, toxicity and compliance of a 5-Fluorouracil, Leucovorin and Irinotecan in combination therapy in patients (pts) with metastatic colorectal cancer

**Materials and Methods** from March 1999 to April 2000, 15 pts, 14 males and 1 female, with metastatic colorectal cancer entered this study (mean age 63 years, range 40-75 , ECOG PS 0, range 0-1). Six pts (40%) were treated as first line treatment; 9 pts (60%) as second line (after treatment with 5FU, LV and/or FUDR) Sites of metastatic disease were: liver 14, lung 6, lymphnodes 4, adrenal glands 3, spleen 2, bones 1. Treatment schedule was: 5FU 1600 mg/m$^2$ continuous i v in 24 hours, LV 500 mg/m$^2$ i.v , CPT-11 80 mg/m$^2$ i v on day 1,8,15,22 with a 14 days interval and repeated on day 36, for a maximum of 8 courses. A total of 54 cycles (median number of cycles/patient 4; range, 1-8) was administered. Toxicity and response were evaluated by WHO criteria; all pts were evaluable for toxicity (at least 1 cycle done) and 13 for objective response, after 2 cycles of chemotherapy. Two pts were not evaluable for response for early discontinuation due to toxicity (1 pt) and for refusal (1 pt), both after first cycle of therapy

**Results:** response and toxicity are reported on the following table

| RESPONSE 13 pts | TOXICITY 15 pts | | |
|---|---|---|---|
| | - Diarrhoea: | G2 = 4 (27%) | G3 = 3 (20%) |
| • PD = 6 (46%) | - Emesis. | G2 = 3 (20%) | G3 = 2 (13%) |
| | - Anemia: | G2 = 1 (7%) | G3 = / |
| • SD – 4 (31%) | - Neutropenia | G2 = 1 (7%) | G3 = / |
| | - Mucositis: | G2 = 1 (7%) | G3 = / |
| • PR = 3 (23%) | - Alopecia: | G2 = 1 (7%) | G3 = / |

The median duration of PR plus SD was 7 months (range 3-12+). No significant hematological toxicity, no febrile neutropenia, no treatment-related death were observed. All courses were conducted in a outpatient setting. No hospitalisation occurred

**Conclusions:** preliminary results suggest a relative activity of this combination regimen, with an acceptable patients compliance due to low toxicity. Accrual is ongoing

## H23 SEMI-INTERMITTENT 48 HOURS INFUSION 5-FLUOROURACIL (5-FU), ASSOCIATED WITH LEUCOVORIN (LED), EPIRUBICIN (EPIDX) AND CISPLATIN (CDDP) IN METASTATIC GASTRIC CARCINOMA (MGC): A PHASE II STUDY.

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PELF regimen (5-FU + LED + EPIDX + CDDP) is an active combination in MGC although associated with moderate toxicities. We have recently demonstrated that the semi-intermittent infusion of 5-FU improves tolerability and allows dose escalations. In "in vitro" studies we have also demonstrated that the administration of CDDP after 5-FU improves the synergism of the two drugs. A phase II study with semi-intermittent PELF was therefore initiated in patients (pts) with MGC. o far 31 pts entered the study. Pts characteristics were: MJF.2318, median age: 61 years (range 42-70), median ECOG PS: 0 (range 0-i), single metastatic sites in 12 pts, multiple in 19, previous chemotherapy: 3 pts. The treatment consisted of EPIDX 60 mg/sqm day 1 i.v. bolus, LED 250 mg/sqm over 2 hours i v. infusion followed by 5-FU 3500 mg/sqm as a 48 hours continous semi-intermittent infusion (with 67% of 5-FU doses administered between 4.00 pm and 12.00 pm), CDDP 60 mg/sqm i.v. bolus day 3. Cycles were repeated every 21 days. All pts were evaluable for toxicity. Treatment was well tolerated and among 157 cycles administered WHO grade III-IV toxicity were: stomatitis: 2.5%; diarrhoea. 0.6%.; anemia: 2.5%; leukopenia: 5.7%. Twenty-five percent dose reduction was required in 10 pts. No toxic deaths occurred. Twenty-five pts were evaluable for response (4 too early, 1 peritoneum, 1 pt stopped CT after 1 cycle because of toxicity). We observed 4 complete responses, 9 partial responses, 7 stable disease and 5 progression of disease. The response rate was 52% (95% C.L: 31.3-72+2 %)).These results indicate that the treatment with semi-intermittent PELF we used has significant activity in MGC and is well tolerated.