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Biweekly irinotecan (IRI) with 6s-folinic acid (FA)-modulated 5-fluorouracil (FU) i.v. bolus in advanced colorectal carcinoma (ACC): a phase III study

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Purpose: In our previous studies we have established that IRI can be combined with FA-modulated FU i.v. bolus every 2 wks, producing an interesting response rate (RR) in ACC. The aim of this study was to compare the activity and toxicity of this new regimen with doubly-modulated FU.

Methods: Pts with measurable ACC were randomly allocated to receive: IRI 200 mg/m2 (1-h i.v. infusion) on d 1, FA 250 mg/m2 (2-h i.v. infusion) + FU 850 mg/m2 (i.v. bolus) on d 2 q 2 wks (IRIFAFU), or MTX 750 mg/m2 (2-h i.v. infusion) on d 1, FA 250 mg/m2 (2-h i.v. infusion) + FU 800 mg/m2 (i.v. bolus) on d 2 q 2 wks (MTXFAFU). RR and time to progression (TTP) were the main end-points of this study.

Results: From June 1998 to December 2000, 234 eligible patients were enrolled: median age 63 (range, 29-79) yrs; M/F=136/98; ECOG PS 0/1/2=138/85/11; colon/rectum=168/66; previous adjuvant FAFU=65; disease sites 1/2/*3 = 130/78/26; liver/lung mets=167/52. As of March 31, 2001, confirmed responses were 41 (9 CRs) with IRIFAFU (RR=35%), and 23 (4 CRs) with MTXFAFU (RR=20%) ($p<0.02$); control of tumor growth was obtained in 60% and 48% of pts, respectively, ($p<0.05$). Median TTP was 7.3 vs 4.4 mo. ($p<0.03$). With 48% of pts censored, survival data are not mature yet. 976 courses of IRIFAFU and 795 of MTXFAFU were analysed for WHO toxicity: grade 3-4 neutropenia was reported in 41% and 10% of pts ($p<0.001$), and diarrhoea in 13% and 4% of pts ($p<0.001$), respectively.

Conclusion: Our IRIFAFU regimen is comparable with other weekly or biweekly combinations in terms of both activity and toxicity; however, our IRIFAFU is time-sparing, and it does not require expensive pumps or infusional devices, so improving both patients and doctors compliance to treatment.

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Oxaliplatin (L-OHP) and irinotecan (CPT-11) with 6s-leucovorin (IFA)-modulated 5-fluorouracil (FU) i.v. bolus every 2 weeks: a dose-finding study in patients (pts) with gastrointestinal malignancies

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Purpose: Both CPT-11 and L-OHP are active drugs in first as well as second line treatment of advanced colorectal cancer pts, their toxicity profiles are not overlapping, and they have shown synergism with LFAFU. We planned this phase I study to define the dose limiting toxicity (DLT), and the maximum tolerated doses (MTD) of a triplet regimen of L-OHP+CPT-11+LFAFU given every 2 weeks.

Methods: At least 3 pts were entered at each dose level, and study proceeded if no more than 33% of pts showed DLT after the 1st cycle. Starting doses of L-OHP and CPT-11 were 85 mg/m2 and 150 mg/m2, respectively, and they were alternately escalated to 110 mg/m2 and 200 mg/m2. After reaching the MTD, LFA and FU were added on day 2 to the previous dose level, starting with 250 mg/m2 (fixed dose, 2-h i.v. infusion) for LFA, and 650 mg/m2 (i.v. bolus) for FU.

Results: 38 pts with pretreated gastrointestinal carcinomas (colorectal, 33, other, 5) were entered this trial. Along the first 3 steps, doses of L-OHP and CPT-11 were safely escalated up to 110 mg/m2 and 175 mg/m2, respectively, every 2 wks, with only 4/21 pts suffering DLT (G 3 diarrhoea, 3 pts, > 1 week delay, 1 pt). L-OHP 110 mg/m2 plus CPT-11 200 mg/m2 were considered the MTDs, because 3/6 pts had DLT (G 4 diarrhoea in 2 pts, G 3 diarrhoea plus G 4 neutropenia, 1 pt) after the 1st cycle. In the 11 subsequent pts, LFA-modulated FU was safely administered at 650 mg/m2 (6 pts), or 800 mg/m2 (5 pts): no pt showed G * 3 toxicity. So far, 2 CRs, 4 PRs, and 1 MR were achieved among 30 assessable pts (4 pts were NED before CT, and 4 are TE) giving a response rate of 20%.

Conclusions: L-OHP 110 mg/m2 + CPT-11 175 mg/m2 on day 1, followed by LFA 250 mg/m2 + FU 800 mg/m2 i.v. bolus on day 2, is a safe and active regimen to be given every 2 weeks in retreated ACC.

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Hepatic arterial chemotherapy of 5 fluorouracil (5FU) combined with intravenous 5FU and folinic acid in patients with liver metastases of colorectal cancer

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Purpose: The hepatic arterial chemotherapy is an effective regional treatment for colorectal liver metastases. In our study, we evaluated the combination of 5FU arterial with intravenous 5 FU and folinic acid.

Methods: 23 patients with unresectable colorectal metastases confined to the liver were treated following this schedule repeated every four weeks: 5 FU in the hepatic artery at a dose of 800 to 1000 mg/m2/day by continuous infusion for 4 days combined with folinic acid (20mg/m2/day) followed by 1 hour intravenous infusion of 5 FU (400 mg/m2/day) for 4 days.

Results: One complete response (5%) and 8 (35%) partial responses were observed, objective response rate: 40%. For five patients liver metastases were secondarily resected. Median survival was 16 months. The initial site of progression was liver alone in 26% of the patients, liver and others sites in 13% and not in the liver in 13%.Grade 3-4 toxicity were: neutropenia in 11 patients (46.8%) with one treatment related death, and mucositis 8 patients (34,8%). Nine patients stopped treatment because of a complication of catheter: thrombosis (n=8) and dislocation (n=1).

Conclusion: The combination of hepatic intraarterial and intravenous chemotherapy with 5 FU gave a response rate of 40% for patients with unresectable liver metastases. The evolution of disease in extrahepatic site was only observed in 26% of patients.

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Phase II trial of irinotecan (CPT-11) plus raltitrexed (ZD) in patients with previously untreated, advanced colorectal cancer (ACC)

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Background: The combination of CPT-11 plus ZD has shown its security and efficacy as a second line chemotherapy in patients with ACC after the failure to a fluoropirimidine schedule (Cuningham D, EJC 1999; Aparicio J. ESMO 2000). Also, recent data seem to confirm its activity in first line chemotherapy (Carnaghi C, ASCO 2000). The primary objective of this study was to assess the security, efficacy and survival time achieved with a three-week administration of this combination.

Patients and methods: From May 2000 to March de 2001, 63 patients were enrolled and treated with CPT-11 (350 mg/m2 as a 60-minute infusion) and ZD (3 mg/m2 in a 15-minute infusion, 1hour after CPT-11) every 21 days. 43 patients are currently available for toxicity assessment and 29 for efficacy analysis. Baseline characteristics: 29% females and 71% males, with a median age of 62 years (range, 39-76). Performance Status: 0 in 46% of cases, 1 in 42%, and 2 in 12%. 34% of patients presented more than one organ affected (liver 60%, lung 4,8%, liver + lung 12%, and liver + others 13%). Only 9 patients had been treated with adjuvant therapy, and only 6 had been irradiated.

Results: 197 infusions have been administered to the first 43 patients, with a median of 5 per patient (1-14). Of them, 2.54% have been delayed due to toxicity and 2.54% required dose reduction due to the same reason, achieving a relative dose intensity of 0.94. Main grade 3-4 (GALCB) toxicity per patient has been: alopecia (32,6%), diarrhoea (18,6%), asthenia (5,3%), neutropenia (11,6%) including 9,3% of neutropenic fever, nausea and vomiting (9,3%), anaemia (9,3%) and hepatic toxicity 9,3%. 29 patients have been evaluated for efficacy: 8 achieved objective responses (28%, 2 complete and 6 partial responses), 13 maintained stable disease (44%) and 8 progressed (28%).

Conclusions: According to these preliminary results, the combination of CPT-11 and ZD presents a manageable toxicity and remarkable tumour growth control (72%) in the population studied. If such data are confirmed, this schedule may become an alternative to more complex regimens in the first line treatment of ACC.