occurred in 4 out of 6 pts at 25 mg/sqm and in 2 out of 4 pts at 22.5 mg/sqm; this last dose of CPT-11 (22.5 mg/sqm) was defined as MTD. Pharmacokinetic analysis demonstrated a Cmax and AUC of 0.034 mg/L and 3.635 hxmg/L respectively for CPT-11 and of 0.065 μg/L and 0.155 hxmg/L respectively for SN-38. This mean value of SN-38 AUC was 43% greater than that we had previously calculated in patients who had received CPT-11 at the same dosage in a 60 - infusion (0.108 hxmg/L). Twelve patients are evaluable for response and 3 (25%) partial responses and 2 (17%) minor responses have been observed.

Results: These preliminary results demonstrate that the treatment with CPT-11 seven days c.i. is feasible with diarrhea being the dose limiting toxicity; recommended dose for phase II studies is 20.0 mg/sqm/day. Antitumor activity is promising and encouraging further investigation.

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Phase I study of triple drug combination of CPT-11 (C), Oxaliplatin (O) and Tomudex (T) (COT) in previously untreated metastatic colorectal cancer (MCRC): National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), IND.135

J.A. Maroun[1], D. Jonker[2], L. Seymour[3], R. Goel[1], W. Kocha[2], B. Fisher[3].
[1] *Ottawa Regional Cancer Centre, Medical Oncology, Ottawa, Canada;*
[2] *London Regional Cancer Centre, Medical Oncology, London, Canada;*
[3] *NCIC CTG, Kingston, Canada*

Objectives: C,O,and T are each active as single agents in MCRC. Data on several doublet combinations have demonstrated increased activity in this disease. The objectives of this study are to determine the Maximum Tolerated Dose (MTD), Dose Limiting Toxicity (DLT) and Recommended Phase II Dose (RD) for this triple combination.

Methods: The starting dose of the three drugs was C: 200mg/m2, O: 90mg/m2 and T: 2.75 mg/m2 given I.V. on day 1 repeated every 3 weeks. Patients (pts) with previously untreated MCRC, measurable disease, performance status ECOG <3 and adequate organ function were eligible. Prior adjuvant fluoropyrimidines was permitted. Cohorts of 3 pts were to be treated at each dose level (DL) with escalation based on toxicity.

Results: 16 pts (median age 60 yrs) received 43 cycles. No DLT were seen at DL 1 and 2. At DL 3 (C: 235 mg/m2, O: 105 mg/m2 and T: 2.75 mg/m2), 2/3 pts had DLT (diarrhea and dehydration despite adequate use of Imodium). No DLT has been noted in 4 evaluable pts at DL 4 (C: 210 mg/m2, O: 100mg/m2 and T: 2.75 mg/m2). Other non-hematological toxicities were mainly grade 1 or 2 and included nausea (10 pts), vomiting (9 pts), anorexia (9 pts), fatigue (8 pts), diarrhea (8 pts) and alopecia (6 pts). Intermittent and reversible grade 1-2 neurotoxicity was common and included 2 pts who received 9 and 11 cycles and consisted mainly of neuro-sensory symptoms with worsening on exposure to cold lasting 7-10 days after therapy. Myelosuppression was generally mild at DL 1 and 2 with 1 grade 3 thrombocytopenia at DL 3 and 1 grade 4 granulocytopenia of short duration at DL 4. There were no significant biochemical abnormalities other than expected grade 3 elevation in transaminases. 1 pt died due to intra-abdominal disease progression during cycle 1 with bowel obstruction, vomiting and aspiration pneumonia with respiratory distress; this pt also had drug related early vomiting and myelosuppression. 7 pts are currently evaluable for response with 4 partial responses.

Conclusion: Triple drug combination with COT is feasible with manageable toxicity. DLT consisted of diarrhea and dehydration. Pts are presently accruing at DL 5 (C: 220 mg/m2, O: 100 mg/m2 and T: 2.75 mg/m2) in order to define the RD. There is evidence of activity in untreated MCRC; a formal phase II study is planned.

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A phase II study of weekly irinotecan (CPT-11) and oral uracil and ftorafur (UFT) plus folinic acid (FA) as first line treatment in advanced colorectal cancer (CRC)

J. Cruz[1], M. Mendez[2], P. Alfonso[3], E. Gonzalez[4], E. Pujol[5], C. Castañon[6], P. Cerezuela[7]. [1] *H Universitario de Salamanca, Medical Oncology, Salamanca, Spain;* [2] *H de Mostoles, Medical Oncology, Madrid, Spain;* [3] *H Gregorio Marañon, Medical Oncology, Madrid, Spain;* [4] *H Virgen de las Nieves, Medical Oncology, Granada, Spain;* [5] *H Rio-Hortega, Medical Oncology, Valladolid, Spain;* [6] *H Virgen Blanca, León, Spain;* [7] *H Naval del Mediterráneo, Cartagena, Spain*

Purpose: The aim of this prospective phase II study was to determine the efficacy and toxicity profile of weekly CPT-11 and oral UFT/FA as first line treatment of advanced CRC.

Patients and methods: Patients with advanced CRC, not treated previously with chemotherapy for metastatic disease, at least 1 bidimensionally measurable lesion, ECOG PS < or = 2 (patients older than 75 years ECOG PS < or = 1) and with adequate bone marrow, renal and hepatic function were included in the study. Exclusion criteria were previous treatment with any topoisomerase I inhibitor, or any intestinal pathology. Patients were treated with CPT-11 (125 mg/m2) given as an iv 90-minutes infusion, on days 1, 8 and 15 and UFT (200 mg/m2/day) plus FA (45 mg/day) given orally on days 1-21. Cycles were repeated every 4 weeks until progression, unacceptable toxicity or consent withdrawal.

Results: Thirty-four patients were enrolled (M/F, 19/15) with a median age of 62 years old (44-80). ECOG PS was 0-1 in 82% of patients. Primary tumor sites were colon (21) and rectum (13). Histology was adenocarcinoma in all cases. Previous treatment included surgery (100%), radiotherapy (23%) and adjuvant chemotherapy (39%). Median number of involved sites was 1 (41% with 2 sites or more) located in liver (74%), lung (21%), lymph nodes (12%), skin (3%) and bone (3%). A total of 141 cycles (median 5, range 1-6) and 430 infusions (median 15, range 2-18) were administered to 34 patients, all of which were evaluable for toxicity. Grade III/IV neutropenia was observed in 2 cycles (1%) and febrile neutropenia in 1 cycle (1%). No other grade III/IV hematologic toxicity was reported. Late diarrhea (6% of cycles), nausea and vomiting, fever without neutropenia, allergic reaction, tenesmus and colic pain in 1% of cycles were the only grade III/IV non-hematologic toxicities observed during the study. Efficacy: Four patients were considered not evaluable for efficacy due to 2 adverse events (allergic reaction and gastrointestinal intolerance), 1 early death (cardiac insufficiency) and 1 consent withdrawal. Of 30 patients evaluable for efficacy, 1 achieved CR, 9 PR, 11 SD and 9 progressed resulting in an ORR of 33% (CI 95%: 16-50). Median time to progression and duration of response was 7.0 months (CI 95%: 5.7-8.3) and 4.9 months (2.7-7.2), respectively.

Conclusion: Weekly irinotecan in combination with oral UFT/FA is active as first line treatment in advanced CRC with a manageable toxicity profile.

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A phase II study of biweekly irinotecan (CPT-11) and 5-fluorouracil (5-FU) as first line treatment in advanced or metastatic colorectal cancer (CRC)

J. Salvador[1], R. Bernabe[1], M. Bolaños[2], P. Borrega[2], M. Valladares[3], M. Cobo[4], J. Reina[5], M. Gomez-Reina[6], P. Gallurt[7], J. Moreno-Nogueira[1]. [1] *H Virgen del Rocio, Medical Oncology, Sevilla, Spain;* [2] *H San Pedro de Alcantara, Medical Oncology, Caceres, Spain;* [3] *H Juan Canalejo, Medical Oncology, A Coruña, Spain;* [4] *H Carlos Haya, Medical Oncology, Malaga, Spain;* [5] *H Juan Ramon Jimenez, Medical Oncology, Huelva, Spain;* [6], *H Puerta del Mar, Cádiz, Spain;* [7], *H de Puerto Real, Cádiz, Spain*

Purpose: To evaluate the efficacy and safety profile of a biweekly combination of CPT-11 and 5-FU as first line chemotherapy in patients with advanced or metastatic CRC.

Patients and methods: Patients with histologically confirmed CRC, without previous chemotherapy for metastatic disease, at least 1 bidimensionally measurable lesion, ECOG PS < or = 2 and with adequate bone marrow, renal and hepatic function were eligible for this study. Exclusion criteria were previous treatment with any topoisomerase I inhibitor and any other intestinal pathology. Patients were treated with CPT-11 (150 mg/m2) given as a 90-minutes iv infusion, on days 1 and 15 followed by a four-day continuous iv infusion of 5-FU (1000 mg/m2/day) on days 1-4 and 15-18 every 4 weeks until progression, unacceptable toxicity or consent withdrawal.

Results: Eighty-two patients were enrolled (M/F, 50/32). Median age was 61 years (35-78). The ECOG PS was 0-1 in 99% of patients. Primary tumor sites were colon (48) and rectum (34). Tumour histology was adenocarcinoma in all cases. Previous treatment included surgery (99%), radiotherapy (17%) and adjuvant chemotherapy (30%). Median number of involved sites was 2 (76% with 2 sites or more).A total of 354 cycles (median 4, range 0-12) and 719 infusions (median 8, range 1-24) were administered to 82 patients with a median relative dose intensity of 90% and 89% for CPT-11 and 5-FU, respectively. All patients were evaluated for safety analysis. Grade III/IV hematologic toxicity per cycle included neutropenia (1%). Febrile neutropenia was observed in 1 cycle. Grade III/IV non-hematologic toxicity per cycle included mucositis (6%), late diarrhea (2%), nausea (2%), vomiting (1%) and asthenia (1%). Efficacy: At the moment, 10 patients are still undergoing treatment and 6 were considered not evaluable for efficacy due to adverse events in 3 patients (mucositis grade IV, cardiac toxicity and fever), death in 2 patients (cardiac failure and sudden death) and consent withdrawal in 1 patient. Of 66 patients evaluable for efficacy, 6 achieved CR, 19 PR, 30 SD and 11 progressed resulting in an ORR of 38% (CI 95%: 26-50). Median