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.

1089 POSTER

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

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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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1090 POSTER

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)

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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.

1091 POSTER

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)

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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

time to progression and duration of response was 8 months (6-10) and 6 months (IC 95%: 5-7) respectively. To date, median survival time has not been achieved yet.

Conclusion: Biweekly combination of CPT-11 and 5-FU is an active and well tolerated regimen as first line chemotherapy in advanced or metastatic CRC.

1092 POSTER

CD97 expression in colorectal carcinomas and tumour cell lines

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CD97, a member of the EGF-like domain/seven-span transmembrane (EGF/TM7) family, is present in thyroid carcinoma cell lines but only at low level in normal thyroid epithelial cells. In thyroid carcinoma, CD97 expression correlates with the stage of differentiation and metastasis (Cancer Res. 1997). So far, there have been no studies on the detection of CD97 in other tumour cell lines or entities.

16 out of 16 (16/16) colorectal tumour cell lines investigated were CD97+, although the density of the molecule varied considerably. 15/16 also carried the ligand of CD97, CD55, but most cell lines showed weak or no expression of EMR-2, another closely related member of the EGF/TM7 family. The density of CD97 correlates with the in vitro invading potential and the immunohistological determined proliferation index. TGF-b down-regulates CD97 expression by 25 to 50% in the TGF-b sensitive-cell lines, LS1034 and LS513, but only slightly or not at all in insensitive cell lines such as Colo205 and WiDr.

We also examined 72 colorectal adenocarcinomas and corresponding normal tissues by immunohistology. The monoclonal antibody (mab) CD97EGF detects an epitope at the first EGF-like domain of the molecule, whereas the CD97stalk mab binds to the stalk region right before the transmembrane region. An immunoreactive score was set up based on the method devised by Remmele (RS 0-12).

CD97EGF was detected in 53/72 (mean ± SEM; RS 3.2 ± 0.4) and CD97stalk in 64/72 (RS 5.3 ± 0.3) of the carcinomas. The significant difference in the staining intensity between the CD97EGF and CD97stalk epitope is not caused by different affinities of the used mab, as CD97EGF showed the same or even a stronger staining as CD97stalk in 18/72 cases. The corresponding normal tissues were CD97- for both epitopes, or expressed CD97 more weakly than the tumours (RS 0.8 ± 0.1). Poorly differentiated or scattered cells within one tumour (28/72) were more strongly positive for CD97stalk (RS 10.0 ± 0.4) compared to the cells growing in tubular structures (RS 5.5 ± 0.5). The tumour cells of the invasion margin showed the strongest immune reaction. Dukes stage and preoperatively determined sCD97, CEA, CA15-3, and CA19-9 in the sera of the patients showed no correlation with the expression of CD97 in the tumours.

Taken together, colorectal carcinomas and cell lines express CD97. The different epitopes of the molecule showed varying distributions within the tumours.

1093 POSTER

CPT-11 in combination with capecitabine as first line chemotherapy for metastatic colorectal cancer (MCRC): preliminary results of a phase I/II study

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CPT11, Campto (C) in combination with intravenous (iv) 5 Fluorouracil (5-FU) modulated by folinic acid (FA) is the reference treatment in first line MCRC. Capecitabine, Xeloda (X) is an oral fluoropyrimidine, which is converted to 5-FU predominantly at the tumour site by exploiting the higher activity of thymidine phosphorylase in malignant tissue. It has demonstrated superior activity and improved tolerability compared with iv bolus 5-FU/FA. The convenience of oral administration brings a new alternative to current iv therapy. C and X have different mechanisms of action and are synergistic. A phase I study was conducted to assess the maximum tolerated dose (MTD) and the recommended dose (RD) of the combination. Main eligibility criteria: measurable disease, WHO performance status ≤ 2, adequate haematological, hepatic and renal functions. Prior adjuvant chemotherapy with bolus 5-FU was allowed if the interval between the end of adjuvant and study entry was at least 6 months. C was given iv over 30 minutes, day 1, q 3 wks and X, per os twice daily 12 hours apart from d1 to d14, q 3 wks. Dose escalation (mg/m2): level 1 (3 patients, pts/18 cycles, cy) C 200, X 750; level 2 (6 pts/37 cy) C 250, X 750; level 3 (3 pts/24 cy) C 250, X 1000; level 4 (3 pts/20 cy) C 300, X 1000; level 5 (7 pts/25 cy) C 300, X 1250; level 6 C 350, X 1250. The MTD is reached at level 5 based on overall safety profile: grade (G)3 fatigue 2pts; G3 hand and foot syndrome 1pt; G3 diarrhoea 1pt; Febrile neutropenia 2pts. Recruitment in level 4 (RD) is ongoing. Efficacy is encouraging with responses observed at each dose level. A phase II and pharmacokinetic study is planned.

1094 POSTER

Results of a phase II study combining, weekly Irinotecan with pharmacokinetics (PK) adaptation of 5FU "Gamelin"schedule in first line in patients with metastatic colorectal cancer (MCRC)

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No standard schedule of 5FU/folinic acid (FA) is recommended in MCRC treatment. Infusion can be administered monthly, every 2 weeks or weekly. 'Gamelin' schedule associates FA 100mg/m2 bolus IV followed by 5FU over 7 hours (H); 5FU dose was individually calculated on PK samples, with a starting dose of 1300mg/m2. Our phase II study combines this schedule with weekly Irinotecan 80 mg/m2, H0-H1, given 6 weeks out of 7. The primary endpoint of this trial is the overall response rate (ORR).

Patients characteristics: 35 patients (pts) were included, 29 were analysed for safety and 28 for efficacy. Sex ratio M/F 17/12; PS O/1/2 19/6/3pts, median age 61y[43-75], primary tumor site colon 12pts (42%), rectum 13 (45%), rectosigmoid jonction 4pts(14%). Prior treatment: radiotherapy 8pts (27%), adjuvant chemotherapy 10pts (34.5%). Number of involved sites: one 16 pts (55%)/two 13pts (45%), liver metastasis 24pts(82%). 342 weekly infusions were given with a median of 12[2-24]. Treatment delay >7 days were observed in 10 pts (2 for hematological toxicity, 5 for diarrhea, 3 for other reasons). Safety (gr * per pt): diarrhea 6 pts (20.7%)/1 pt(3.4%) (4pts/7 had diarrhea at inclusion); asthenia 4 pt (13.8%)/0, neutropenia 2pts (3%)/0 without febrile neutropenia. One patient had drug interstitial pneumonitis with unknown causality. ORR: CR 1 pt(3.6%), PR 6 pt(21%), SD18 pt(64%) (9/18pts had only 1 evaluation, PR no confirmed), PD 3pt(11%). 2 pts had surgical resection of liver metastases.

Conclusion: Individually adaptation of 5fU allowed high dose escalation (up to 2480mg/m2/wk) combine with Irinotecan, without increase toxicities and with a good response rate.

1095 POSTER

Preoperative chemoradiation for rectal cancer. Toxicity, downstaging and complications in 114 patients

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Purpose: To define toxicity, surgical morbidity and downstaging in patients (pts) with rectal cancer treated with adjuvant radiochemotherapy followed by curative surgery.

Methods: From May 1993 to January 2001 114 pts (76 M, 38 F, median age 61 years, range 30-87) with a II-III TNM clinical stage adenocarcinoma of the middle-lower rectum received preoperative radiochemotherapy. Fifty-two pts received RT for a dose of 50.4 Gy in 28 fr. along with a continuous infusion (300 mg/m2/day) of 5-fluorouracil (5-FU) and a weekly bolus of Carboplatin (70 mg/m2/day). Sixty-two pts received RT for a dose of 45 Gy in 25 fr., while 5-FU (350 mg/m2/day) and LV (10 mg/m2/day) bolus were administered on days 1-5 and 29-33 during RT. Toxicity was scored according to the RTOG scale.

Results: Sixty-seven pts (58.7%) experienced gastrointestinal toxicity (grade 1-2 in 48 and gr. 3 in 19), 54 pts (47.3%) haematological toxicity (gr.