

Results: Median follow up was 56 months for all living patients in INT1 and INT2a. In the subset of patients receiving 45 Gy with rectal tumors 6cm from the anal verge (INT1: n=143; INT2a: n=52; INT2b: n=29), there was a significant improvement in SP with the use of concurrent chemotherapy (41% at INT1 compared to 13% at INT2, $p < 0.0001$). This finding was supported by a 38% SP rate in the INT2b group. A logistic regression analysis evaluating clinical prognostic factors (gender, year of treatment, diagnostic grade, tumor downstaging, circumferentiality, and length) confirmed that concurrent chemotherapy was the only independently significant factor influencing SP ($p < 0.032$). RFS and LC were not significantly different between INT1 and INT2a. Follow-up for INT2b is insufficient to analyze these endpoints.

Conclusions: The use of concurrent 5FU with preoperative radiotherapy for T3 rectal cancer independently increases SP in low rectal cancer. RFS and LC appear to be unaffected.

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POSTER

Distinct prognostic value of p53 overexpression and gene alterations in colorectal cancer

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Introduction: Prognostic value of p53 mutations in colorectal cancer (CRC) is still controversial.

Objective: To assess the short-term prognostic value of p53 protein overexpression and gene mutation in CRC.

Patients and methods: Between 1/96 and 12/98, 512 patients (pts) were diagnosed with CRC. Among them, 419 had tumor tissue samples available for genetic tests. The present study is restricted to 126 pts. Mean age 67 years, 59% were male. Tumors were located in colon 68% and rectum 32%. Stage was I:11%, II:40%, III:36%, IV:13%. Pts with initial stage IV were excluded. Median of follow up was 25.5 months. Mutations in p53 at exons 5-9 were detected by PCR/SSCP and sequencing. p53 protein overexpression was analysed by IHC using antibodies DO-7. Also mutations in the K-ras oncogene were available. Cox proportional hazards models were used to assess association with disease-free survival and to estimate hazards ratio and 95% confidence intervals.

Results: Overexpression (O+) in p53 protein was evident in 75% of the tumours. Mutation (M+) in p53 gene were founded in 55% of the tumours. Agreement between results was: 52% both positive (O+M+) and 14% both negative (O-M-). Major disagreement was overexpression without mutation: 27% (O+M-). Only 6% were mutated and did not overexpressed protein (O-M+). Overall, p53 mutations did not associate with worse prognosis (HR=0.9/0.5-1.5). However, a trend was observed towards shorter survival in tumours overexpressing p53 protein (HR=1.6/0.9-3.0). Discordant cases (O+M-) showed poorer prognosis than negative concordant (O-M-) HR= 2.1 (0.7-5.8). K-ras mutations were detected in 38% of the cases. Mutations in K-ras were independent of p53 alterations and also showed a trend towards poorer prognosis, HR=1.3 (0.9-1.9).

Conclusions: This preliminary analysis has shown that prognostic value of p53 protein overexpression is higher than that of p53 gene mutations. In the absence of detected gene alterations p53 protein overexpression depicts a group of CRC tumours with poorer outcome.

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POSTER

Any usefulness of oncofoetal markers (CEA and CA19-9) in the management of chemotherapy (CTH) of patients (PTS) with metastatic colo-rectal carcinomas (MCRC)?

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Purpose: CT scan is accepted as gold standard for evaluation of response to CTH in MCRC. The potential helpfulness of less aggressive and expensive procedures, i.e., CEA and CA19-9 dosages, was prospectively investigated.

Methods: From 03/97 to 01/99, radiological tumor response was assessed using spiral CT scan of the thorax abdomen and pelvis every 2 or 3 CTH courses (8 weeks) until disease progression and for a maximum of 5 consecutive visits in 91 consecutive pts receiving 1st (82.4%) or 2nd line CTH for MCRC. At each visit, CEA and CA 19-9 dosages were performed.

Results: CEA and CA19-9 values are available at baseline in 91 and 89 patients and upper the normal value in 78 (85.7%) and 62 (69.7%) respectively. According to the RECIST response criteria (J Natl cancer Inst 2000; 92:205-16), the response rates are: CR=3, PR=22, NC=25, PD=41. In the majority of patients, the response status was determined during the first evaluation (visit #2). The percentage of relative variation of the CEA and CA19-9 values between visits #1 and 2 poorly correlates to tumor response. In fact, a decrease is even observed in 55% of NC and 44% of PD pts with CEA (60% and 45% with CA 19-9). However, all 12 pts experiencing a more than 3 fold increased CEA and/or CA 19-9, regardless the baseline value, are classified as PD.

Conclusion: The use of tumor markers cannot be recommended for tumor response evaluation. Only 13% pts who present a 3 fold increase of CEA and/or CA 19-9 can be considered as PD without the need of a radiological confirmation. Taking into account the hospital costs, the cost benefit ratio of the use of tumor markers in addition to CT scan versus CT scan alone is minus 30400 FF (4635 euros).

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POSTER

Anemia in colorectal cancer patients: a prognostic parameter

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Anemia is a common finding in cancer patients. In a variety of human malignancies the prognostic value has been demonstrated already. In colorectal cancer, however, these studies have not yet been performed. Therefore, the aim of the present study was to compare preoperatively obtained hemoglobin blood levels with various clinico-pathological findings in a series of 485 consecutive colorectal cancer patients treated at the Department of Surgery, University Hospital Innsbruck, between 1992 and 1999.

Blood hemoglobin concentrations ranged from 5.7 g/dl to 18.1 g/dl. 132 out of 485 (28%) patients were anemic (hemoglobin levels ≤ 11 g/dl) prior to operation. Hemoglobin values were statistically significantly related to gender ($P < 0.0001$), tumour site ($P = 0.0001$), pT stage ($P < 0.01$) and tumour stage according to UICC ($P < 0.001$). Anemia was more frequently diagnosed in female (33%) than in male (22%) patients. 58 out of 140 (41%) patients with tumours of the right hemicolon were anemic, whereas the remaining patients showed anemia in only 21% (74 out of 345). The proportion of anemic patients increased with pT stage. 10% of pT1, 21% of pT2, 29% of pT3, and 38% of pT4 tumours showed anemia. 30% of patients were found anemic in tumour stages II, III, and IV according to UICC. In contrary, only 14% were anemic in tumour stage I. Furthermore, anemia was associated with shorter survival times in colorectal cancer patients ($P < 0.001$) and Hazard rate ratios showed that anemia increased mortality by 53% (95% CI 15% - 103%).

The results of the present study strongly support the prognostic value of anemia in human malignancies. Further studies are required to evaluate the impact of anemia treatment on survival.

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POSTER

A phase I and pharmacokinetic study of irinotecan given as a 7 days continuous infusion in metastatic colorectal cancer patients pretreated with 5-FU or raltitrexed

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Rationale: Irinotecan (CPT-11) is a cell cycle specific drug which, binding to topoisomerase I-DNA complex, causes single strand-breaks. However this is a reversible process and it is necessary that the topoisomerase I-DNA-SN-38 cleavable complex remains stable until the DNA replication fork reaches it to result in an irreversible double-strand break. This process may require several hours or days and therefore, although CPT-11 and SN-38 have terminal half-lives of approximately 12 and 24 hours respectively, a more prolonged exposure might enhance the formation of lethal double-strand breaks and cytotoxicity. Experimental studies also support this hypothesis.

Purpose: We have initiated this phase I study to determine the plasma pharmacokinetic and the maximum tolerable dose (MTD) of CPT-11 administered as a 7 days continuous infusion every 21 days in metastatic colorectal cancer patients pretreated with 5-FU or raltitrexed.

Results: Thirteen patients (pts) have entered the study. Three have received CPT-11 at 20 mg/sqm/day, 4 at 22.5 mg/sqm/day and 6 at 25 mg/sqm/day. Dose-limiting toxicity was WHO grade III-IV diarrhea which

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 hmg/L respectively for CPT-11 and of 0.065 μ g/L and 0.155 hmg/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 hmg/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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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 \leq 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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POSTER

A phase II study of weekly irinotecan (CPT-11) and oral uracil and fluorouracil (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 \leq 2 (patients older than 75 years ECOG PS \leq 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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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 \leq 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