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A multicenter prospective phase II study of oxaliplatin (OXA), 5-fluorouracil (5FU) and leucovorin (LV) followed, by irininotecan (IRI), 5FU and LV after progression, in patients (pts) with untreated metastatic colorectal carcinoma (MCRC)

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The combinations of OXA or IRI with 5FU-LV are used as standard treatment in pts with MCRC. However, the right sequence in first or second line is not well defined. We developed a multicenter trial in first-line MCRC, with OXA 85 mg/m2, LV 400 mg/m2, 5FU 400 mg/m2 bolus and 5FU 2400 mg/m2 46h continuous infusion, repeated every 2 weeks. Twelve cycles were scheduled. The treatment could be continued in case of clinical benefit. The objective response was evaluated every six cycles. When progression was observed, patients received IRI 180 mg/m2, LV 400 mg/m2, 5FU 400 mg/m2 bolus and 5FU 2400 mg/m2 46h continuous infusion. From August 2001, 86 pts were enrolled in this trial. The main pts characteristics are: median age 62 years (range 28-76), female/male 36%/64%, primary colon/rectum: 68%/32%, performance status 0-1: 90%, prior adyuvant CT: 21%, number of metastatic sites *geq*: 39%, metastatic liver only: 48%. The number of cycles administered were 621 (median number of cycles/patient: 7; range 1-17). There were 82 patients evaluated for toxicity. The most frequent NCI grade * adverse events, by pts were: neutropenia 17%, diarrhoea 3%, nausea and vomiting 4%, asthenia 3%, hand-food syndrome 1%, constipation 1%, neurotoxicity 11%. Grade 2 neurotoxicity was observed in 28 pts (41%). No toxic death took place. Response was evaluated in 60 pts; 2 had a complete response (CR) and 39 had partial responses (PR), with an objective response rate of 68% (CR 3%, PR 65%), a stable disease rate of 15% and a progression rate of 17%. The median time to progression was 9,4 months (95%CI: 7,7-11). Surgical resection of liver metastasis was performed in 5 pts, after partial response. So far, 17 pts have received second line treatment. This regimen is active and has manageable toxicity as treatment in MCRC.

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Site of intracellular expression of beta-catenin influences the outcome in sporadic colorectal cancer

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Background: Stabilisation and nuclear translocation of beta-catenin are suggested to be the early events in the colorectal carcinogenesis. Nuclear accumulation of beta-catenin was associated with high-grade tumour and increased cell proliferation in epithelial cancers. The aim of our study was to correlate the effects of nuclear and cytoplasmic beta-catenin expression in patients with sporadic colorectal cancer cases with clinical outcome.

Method: Immunohistochemistry was performed on 161 histologically proven colorectal cancer cases and were assessed quantitatively.

Results: Out of 161 samples, 139(86.34%) had over expressed beta-catenin either in the nucleus 54(33.54%), cytoplasm 50(31.06%) or both 35(21.74%). Nuclear expression of beta-catenin was significantly associated with well-differentiated tumours (OR=3.14 p=0.015 CI= 1.25-7.87) and early T' stage disease (OR=2.77 p=0.017 CI= 1.20-6.43). Strong cytoplasmic expression was significantly associated with nodal involvement (p=0.054 χ^2 test), liver metastasis (p=0.050 χ^2 test) and a non-significant association with metastasis (p=0.08 χ^2 test). Using Cox's proportional hazard model, we found significant association between strong cytoplasmic expression and advanced Dukes stage disease with reduced survival (HR=1.59 p=0.044 CI= 1.01-2.50). Those with beta-catenin in the nucleus as well as cytoplasm did not show any significant association with clinical parameters. There were no significant associations found between age and overexpression.

Conclusion: We demonstrate for the first time, cytoplasmic expression was associated with poor clinical outcome in colorectal cancer whereas nuclear expression had an opposite effect. These data suggest that the site of expression has a significant impact on the disease progression by acting *via* different pathways.

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Neoadjuvant treatment of metastatic liver disease with raltitrexed and oxaliplatin in colorectal cancer patients

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Background: Surgical resection is the most effective treatment for colorectal (CRC) liver metastases (mets), but only a minority of patients (p) are initially candidates for a potentially curative resection. The promising activity that raltitrexed and oxaliplatin have recently demonstrated prompted us to study the value of the combination as neoadjuvant treatment.

Material and methods: Inclusion criteria: synchronous not operable or metachronous liver mets of histologically proven CRC, adequate haematological, cardiac, renal and liver function, informed consent. Other metastatic sites excluded. Three categories of nonresectable disease were defined: large size, multinodularity, ill location. The same treatment for all p, raltitrexed: 3 mg/m^2 (15 min iv infusion) and oxaliplatin 130 mg/m^2 (2 h iv infusion) every 3 weeks. Re-staging after 3 and 6 cycles with CT and MRI. Liver resection was performed in those p whose disease became resectable. From 02/2001 to 12/2002, 30 p were treated. Median age: 64 y. ECOG PS: 0, 13 p; 1: 17 p, 18/ 12 colon/rectal cancer. Mets: synchronous: 18 p, metachronous: 12p, > 5 cm in maximum size: 10 p, multinodularity: right lobe: 13 p, bilateral: 13p.

Results: The number of courses given was 129 (1-6, median 4), RDI (two drugs): 0.99. *Toxicity* (WHO) included: Anemia grade 1-2: 16p. Neutropenia g.3: 1p. Thrombocytopenia g.3: 1p. Vomiting g. 1-2: 12 p, g. 3-4: 2p. Diarrhoea g. 1-2: 3p, g. 3: 2p. Asthenia g. 1-2: 12 p, g. 3: 4p. Peripheral neuropathy g. 1-2: 16 p, g. 3: 2p. Increased transaminase activity g. 1-2: 9p, g. 3: 2 p. *Overall response* (29 p, 1 p < 3 cycles) RECIST: 44.8% (CI 95% 26.7- 62.9%), 2 p CR (MRI) and 11 p PR. SD: 7 p. PD: 9 p. Nine p (30%) underwent laparotomic surgery, 7 p radically resected (77.8%). Median follow-up: 7.8 m. Median overall survival: 13.3 m. Median time to progression nonresectable group: 5.6 m and resected group: 9.7 m., 5 p remain disease-free.

Conclusions: Our data suggest that neoadjuvant raltitrexed and oxaliplatin enables liver resection in a significant number of patients (30%) with initially unresectable liver metastases, with an acceptable toxicity profile.

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Phase 2 study of CT-2103 in patients with colorectal cancer having recurrent disease after treatment with a 5-fluorouracil-containing regimen

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CT-2103 (XYOTAX™) is a tumor-targeted taxane designed to concentrate selectively in tumors. CT-2103 exposes normal organs to conjugated paclitaxel, which is non-toxic in vitro, thus minimizing overall toxicity. CT-2103 showed enhanced efficacy compared to paclitaxel/Cremophor in syngeneic and xenogeneic in vivo tumor models including colorectal tumors and other paclitaxel-resistant cell lines. Conjugation of paclitaxel to poly-L-glutamate enhances aqueous solubility and eliminates the need for Cremophor, resulting in a convenient 10 min infusion. Patients enrolled in the 1st cohort of this multicenter study were heavily pretreated with advanced, measurable colorectal cancer that was resistant to 5-FU/leucovorin. Patients received a conjugated paclitaxel dose of 210 mg/m^2 CT-2103 as a 10 minute IV infusion every 21 days. NCI CTC (v 2) are used for safety assessments. Efficacy was assessed after every 2nd cycle according to RECIST. Sixty patients have been treated. The median age was 63 years (range 34-84) and 60% of patients were male. The median time from diagnosis to start of CT-2103 treatment was 20 months (range 2-94). Fifty-four patients (90%) had received prior CPT-11 and 45 of these patients received CT-2103 <6 months after completing CPT-11 therapy. 87% of patients received 2 or more