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A phase I study of irinotecan (I), gemcitabine (G), and 5-fluorouracil (5-FU) in patients with advanced gastrointestinal cancers

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Purpose: Despite the development of new chemotherapeutic drugs, patients with gastrointestinal malignant tumors still have a poor prognosis. The primary aim of this open-label, monocenter, phase I study was to determine the maximum tolerated dose (MTD) of irinotecan, gemcitabine, and 5-fluorouracil (IGF) triplet therapy in patients with gastrointestinal cancer.

Methods: Patients with unresectable or metastatic gastrointestinal cancer received fixed doses of 5-FU (as a 24-hour infusion) with escalating doses of G (as a 30-minute infusion) and I (as a 90-minute infusion) as follows: level I: I 70 mg/m2, G 1000 mg/m2, 5-FU 2000 mg/m2; level II: I 75 mg/m2, G 1000 mg/m2, 5-FU 2000 mg/m2; level III: I 75 mg/m2, G 1250 mg/m2, 5-FU 2000 mg/m2 on days 1 and 8 every 21 days for a maximum of 6 cycles. DLTs were defined as any WHO toxicity greater than or equal to grade 3.

Results: Thirteen patients (2 in dose level I, 6 in dose level II, and 5 in dose level III) were entered in the study. Of the 13 patients, 1 had gallbladder, 3 each had cholangio- and colorectal, 2 had gastric, and 4 had pancreatic carcinoma. There were 2 female and 11 males, with a median age of 63 years (range, 36-77). Seven patients had no prior treatment, whereas 6 patients received prior first-line therapy with various combinations. A total of 48 cycles were administered. Five patients completed 6 cycles of treatment. Three patients in dose level III had grade 3 leukopenia that resulted in dose reductions or delays. One of these patients was pre-treated with etoposide/leucovorin/5-FU for gastric cancer. Grade 3 nausea/vomiting occurred in 1 patient at dose level III. No grade 4 toxicities were reported. Thus, the MTD for IGF was reached at dose level III due to the DLTs of leukopenia and nausea/vomiting. Other toxicities that occurred in dose levels I or II were grade 2 thrombocytopenia (1 patient), grade 1/2 diarrhea (2 patients), and grade 1 nausea (6 patients) and anemia (1 patient [pre-treated]).

Conclusion: The IGF triplet is a safe treatment option at recommended doses of I 75 mg/m2, G 1000 mg/m2, and 5-FU 2000 mg/m2, that should be considered for further clinical studies in advanced gastrointestinal cancers (i.e. pancreatic cancer).

Colo-rectal cancer

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Folfiri then Folfox or Folfox then Folfiri in metastatic colorectal cancer (MCRC): results of a phase III trial

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Available treatments for MCRC patients (pt) are 5FU/LV (F), irinotecan (I) and oxaliplatine (O). FI and FO demonstrated a high efficacy in this setting. The primary end point of this multicentric trial coordinated by the GERCOR was the overall TTP of each sequence in previously untreated pts. Sequence (Seq) A: Folfiri 180 mg/m* of irinotecan at day 1 (d), followed by 200 mg/m2 of l-LV followed by 400 mg/m* of 5FU bolus and 2,4 g/m2 of 5-FU over 46h, Q2W, until progression, and then Folfox, 100 mg/m2 at d1 followed by the same schedule of 5FU/FA, Q2W. Seq B: Folfox then Folfiri. Pt characteristics were well balanced except for sex ratio (M/F: 62/47 and 80/31 respectively).

ITT population	Sequence A		Sequence B	
	Folfiri 109 pts	Folfox 81 pts	Folfox 111 pts	Folfiri 69pts
ORR	56%	15%	53%	4%
ORR + SD	79%	67%	80%	39%
Grade 3-4 NCI -CTC % of pts (* Specific Levi Scale)				
Nb pts(nb cycles)	110 (1579)	82 (634)	110 (1423)	68 (513)
Neutropenia	25	17	44	31
Febrile neutropenia	6	–	1	1
Alopecia (gr2)	24	9	9	13
Diarrhea	14	5	11	9
Neuropathy* (gr3)	0	20	34	18

In Seq A and Seq B respectively: first line TTP are 8.4 and 8.9 months, and 7 pts and 13 pts have had metastatic surgery with complete microscopic resection, according panel review. According investigator's assessment, preliminary results of TTP after 2 lines of therapy are 14.5 months and 11.9 months, in Seq A and Seq B, respectively. Both Seq are feasible and demonstrate promising activity in terms of disease control.

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NCIC CTG IND.122: a phase I/II pharmacokinetics (PK) and pharmacodynamic (PD) study of zd1839 (iressa™). Final phase I results and preliminary phase II results of ZD1839 (750 mg/day) in patients (pts) with colorectal cancer

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Purpose: To assess PK, PD, toxicity, biologic and objective response of ZD839, an oral epidermal growth factor (EGFR) receptor tyrosine kinase inhibitor, in a 2-part, 3-centre dose escalation study.

Methods: Pts were enrolled to part 1 (dose escalation) or part 2 (expansion in pts with colorectal cancer). Tumour biopsies were planned in all pts at baseline and after 28 days of treatment with ZD1839. EGFR, mutated EGFR expression and activation, p-EGFR, p-ERK, Ki67 and apoptosis were measured.

Results: Twenty-eight pts were entered to 6 dose levels (3 pts: 150 mg/d, 3 pts: 225 mg/d, 4 pts: 300 mg/d, 5 pts: 400 mg/d, 4 pts: 600 mg/d, 9 pts: 800mg/d as single oral doses) in part 1; all were evaluable. Pt characteristics: ECOG performance status (PS) 0/1/2 in 7/16/5 pts, median age 60 yrs, 4 pts had colon, 5 pts NSCLC, 3 pts had endometrial cancer and 16 pts had other cancers. Dose related toxicities included skin rash and diarrhea (usually manageable grade 1 or 2). Three pts had grade 3 diarrhea (1 pt at 300mg, 2 pts at 800mg/day, grade 1 diarrhea at baseline in all pts). One pt had an unconfirmed PR, 2 pts have had minor responses, 1 patient has had continuing stable disease for 10 months (ovarian cancer, 3 prior chemotherapy regimens) all at doses of 600mg and 800mg/day. A dose of 750mg/day was selected for further study, based upon an acceptable toxicity profile and evidence of activity at the two highest dose levels. In part II an additional 20 pts with colorectal cancer are treated with ZD1839 at 750mg/day.

Conclusions: Early data suggest a dose of 750 mg/day is tolerable in pts with colorectal cancer; response data are as yet immature.

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Preliminary results of outpatient hepatic artery brachytherapy for colorectal hepatic metastases

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Purpose: We have developed a multidisciplinary outpatient treatment protocol using Yttrium-90 impregnated glass microspheres (TheraSphere®, MDS Nordion, Ottawa, Canada), delivered to tumors via the hepatic artery. Each sphere is approximately 25 microns in diameter, and becomes embolized around the tumors.

Materials and Methods: Patients were eligible for the study if they had histologic confirmation of colorectal metastasis in the liver, normal CBC, Cr, bilirubin, and predominately liver disease. The treatment team included a Radiation Oncologist, Medical Oncologist, and Interventional Radiologist, who evaluated patients jointly. A hepatic angiogram was performed prior to treatment with a 3D SPECT technetium-99m macroaggregated albumin (99m TcMAA) scan to identify if a significant (>10%) shunt was present to the lung, or any shunt was present to the stomach or duodenum. A spiral CT scan was done with liver volume reconstruction to determine the required source strength (3, 5, 10 or 20 GBq) of 90 Y-microspheres. A target dose of 150 Gy was planned for the whole liver. Each patient was followed with a physical exam, biochemistries and CBC, then monthly or as needed. Imaging studies were done at 6, 12, and 18 weeks post treatment. The first 16 patients received whole liver infusion. The last 3 patients first had the right lobe infused, followed 4 weeks later by treatment of the left lobe.

Results: A total of 19 patients were treated: 15 men, 4 women, with a median age of 62 years, (range 30-88 years). All patients had previously received multiple courses of chemotherapy which contained CPT-11. The median total dose delivered was 143 Gy, (range 108-158). There were no complications during administration of the 90 Y-microspheres and no patient

was lost to follow-up. There have been 4 deaths from disseminated disease, and 4 patients admitted in the first 6 weeks after treatment for various reasons. No patient experienced liver failure or veno-oclusive disease. Responses measured by CEA and CT or MRI scans showed that 25% of patients had at least a >50% reduction in tumor burden; 55% of patients had stable disease or <50% response, and 20% of the patients failed distantly.

Conclusion: Radioactive 90-yttrium microspheres induce a 25% partial response rate in patients with chemo refractory metastases from colorectal cancer. It is a safe and low toxicity outpatient treatment in the dose range reported.

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Sphyncter preserving procedures for low rectal cancer

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Introduction: Total rectal resection (TRR) with coloendoanal anastomosis (CEAA), mesorectum 'en bloc' excision (TME), radical abdomino-pelvic lymphadenectomy (RAPL) and J colic reservoir represents a valid alternative to the traditional surgery for the restorative management of low rectal cancer.

Methods: We report our experience at National Cancer Institute of Milan, Italy with this procedure. From March 1990 to December 2000, 346 consecutive TRR with CEAA were performed at our Institute; 262 patients, with a minimum follow-up of 18 months, were treated for a primary cancer of distal rectum at a distance ranging from 3 to 8 cm within the anal verge. Patient's stratification based on definitive pathological report staging was 64 (20%) Dukes' stage A, 101 (32%) stage B and 155 (48%) stage C.

Results: Overall recurrence rate was 8.7%; (23 patients) pattern of local recurrence according to stage of disease was 3 Dukes' A, 6 Dukes' B and 14 Dukes' C after an interval ranging from 8 and 47 months. A specific pathologic evaluation was performed by a dedicated pathologist (S.A.) in the last consecutive 147 cases.

Blood vessel invasion (BVI) was present in 10 out of 51 No patients. Tumour recurrence occurred in 5 out of 41 BVI+ patients versus 3 out of 41 BVI- patients (2 positive distal resection margin and one positive circumferential margin of mesorectum). Perineural invasion (PNI) was present in 8.8% of 45 Dukes B patients and 41.1% of 73 Dukes C patients (47% N1 and 53% N2). In the 17 PNI+ patients local recurrence occurred in 74% (35% N1 and 65% N2) versus 45% of 15 PNI- patients (40% N1 and 60% N2). Four Dukes A patients and 17 Dukes B patients have distal resection margin (DRM) less than 9 mm (median follow-up 40 months). No recurrence occurred in Stage A patients; 3 Stage B patients had lung metastases (2 BVI+ and one DRM+), one experienced local recurrence (DRM+). Dukes B patients received postoperative radiotherapy.

Conclusion: Our data, in accordance with other authors, seem to highlight that important pathologic prognostic factors turned out to be BVI in No patients, PNI in C patients. DRM less 9 mm plus RT did not influence clinical outcome of No patients.

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Thymidylate synthase and p53 expression do not predict chemotherapy outcome in metastatic colorectal carcinoma

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Introduction: Thymidylate synthase (TS) and p53 have been reported to predict the results from chemotherapy in advanced colorectal carcinoma (ARCR).

Methods: One hundred and twenty-two patients with ARCR have been treated with 5-fluorouracil (5-FU)-based therapy at the University Hospital in Uppsala in four different randomised clinical phase III studies between 1989 - 1997. The paraffin-embedded tumours at primary diagnosis were retrospectively analysed with immunohistochemical technique. TS enzyme levels were evaluated using the monoclonal antibody TS 106 and the p53 expression with the monoclonal antibody DO-7.

Results: Fifty-three (43%) of the patients had advanced disease at diagnosis. There were 26% radiological responders. Seventy-eight % had high TS expression and 60% of the tumours were p53 positive. None of the markers predicted the outcome of the later palliative treatment. However, the TS values had prognostic information and significantly predicted time to recurrence (median for low TS 30 months and for high TS values 11 months, p = 0.001).

Conclusion: Immunohistochemical investigation of TS and p53 of the primary cancer is not useful to predict outcome after palliative chemotherapy in ARCR. TS can instead be regarded as a marker of proliferation.

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Expression of CEACAM6 in colorectal cancer: significant association with overall and disease-free survival

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Members of the carcinoembryonic antigen family,CEACAM1,CEA, and CEACAM6 are co-expressed in normal colorectal epithelia but are deregulated in many colorectal tumors.Very recent studies have shown that human CEACAM1 which is often downregulated in colorectal cancers has tumor suppressive activity in prostate cancer. CEA or CEACAM6 which can block differentiation, disrupt cell polarization and tissue architecture, and inhibit apoptosis (anoikis) are overexpressed in many human tumors. The aim of our study was to investigate a possible relationship between tissue expression of these functionally active molecules and prognosis in patients with colorectal cancer.Patients have been enrolled in a randomized, controlled clinical SAKK study. Immunohistochemical analysis was carried out on tissue microarrays from 240 paraffin embedded biopsies with specific monoclonal antibodies (mabs) against CEACAM1, CEA, or CEACAM6.Staining of tumor microarrays was scored from negative (-) to strongly positive (+++).Long-term overall (OAS) or disease-free survival (DFS) in patients with enhanced (++/+++) or reduced (-/+)individual CEA family antigen expression was calculated by use of Kaplan-Meier estimates and the Cox proportional hazards model.The median follow up time was 13 years. Tissue expression of CEACAM1 was reduced (-/+) in 102 patients whereas CEA and CEACAM6 were enhanced (++/+++) in 226 and 132 patients, respectively.CEACAM1 or CEA showed no significant relationship to overall or disease-free survival of colorectal cancer patients.In the case of CEA, however, only 14 patients showed reduced expression.In contrast, unvariate analysis demonstrated that enhanced expression of CEACAM6 (55.4%) was associated with far worse OAS (hazard ratio = HR, 2.19; p = 0.00014) and DFS (HR, 2.44; p = 0.000029). Multivariate Cox analysis including sex, age, tumor localization, tumor staging, lymph node status, and treatment showed that CEACAM6 overexpression independently predicted survival (OAS, HR, 1.89; p = 0.0027; DFS, HR, 2.00; p = 0.0085).To our knowledge this study is the first to demonstrate the prognostic significance of immunohistologically detectable overexpression of CEACAM6 in patients with resectable colorectal cancer. This may help to identify patients who need to be selected for adjuvant treatments or an intensive postoperative follow-up protocol.The data are in good agreement with recent functional findings.

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Extended phase I study of capecitabine and weekly irinotecan as first-line chemotherapy in metastatic colorectal cancer

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Purpose: Capecitabine (CAP) demonstrated efficacy in metastatic colorectal cancer (CRC). Preclinical data on nude mice bearing human colon tumor xenografts demonstrated significant synergistic antitumor activity for the