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METHOTREXATE, L-FOLINIC ACID AND 5-FLUOROURACIL IN THE TREATMENT OF ADVANCED DIGESTIVE TRACT CARCINOMAS

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In a preliminary study we demonstrated that the dosage of MTX required to achieve a MTX serum level above 1 μM for at least 24 h was 500 mg/sqm i.v. A combination of MTX 500 mg/sqm i.v.(day 1), LFA 250 mg/sqm i.v. + 5FU 600 mg/sqm i.v. (day 2) every 2 wks in the treatment of 94 consecutive pts with advanced gastrointestinal malignancies was demonstrated as effective as other biochemical modulation of 5FU. In addition, a MTX serum level ⩾ 2 μM seemed related to the probability of response. From Sept. 1994 to date, 48 pts affected by advanced carcinoma of the digestive tract were treated every 2 weeks for at least 4 courses with MTX 750 mg/sqm on d.1, LFA 250 mg/sqm + 5FU 800 mg/sqm on d.2. Presently, 29 pts are evaluable for response. Primary site was large bowel in 22, stomach in 4, gall-bladder in 2, and pancreas in 1. Fourteen pts had received a previous systemic chemotherapy, mainly with fluoropyrimidine ± LFA. We obtained 1 CR and 5 PRs (OR 21%). Chemotherapy-naive pts showed an OR in 33% of cases (stomach 33%, colon-rectum 40%), while responses were reported in 7% of previously treated pts. The most common acute toxicities were mucositis (WHO G 3–4 in 6% of courses and 19% of pts), and leucopenia (5% and 15%).

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PHASE II STUDY OF CRYOTHERAPY FOR HEPATIC TUMOURS

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Over an 18-month period we have performed hepatic cryotherapy for, liver tumours on 29 occasions in 28 patients (14 males, median age 59 [38–73] years. Two patients had multifocal primary tumours (hepatoma and cholangiocarcinoma); 26 had metastases: 23 colorectal cancer (nine combined with resection); two carcinoid and one renal carcinoma. Between 1–14 (median 4) lesions were treated per patient. Median hospital stay was 7 (4–43) days with 28% operative morbidity and one 30-day death from myocardial infarction. Both patients with carcinoid obtained complete relief of symptoms and remain so at 6 and 12 months. Both patients with primary disease and the patient with renal carcinoma area dead. Of the 23 patients with colorectal cancer, three are disease free (6, 8, 15 months after surgery), all with <4 lesions treated. Twelve patients with 4–10 lesions treated, achieved a partial response (>50% tumour reduction) and are well, 3–15 months after surgery. Eight patients had >10 lesions treated and none showed a response; five are now dead. In conclusion, hepatic cryotherapy may offer an adjunct to hepatectomy in patients with carcinoid and colorectal liver metastases. However, in the latter group it should be confined to patients with <10 metastases and should only be considered as a possible curative treatment for three or fewer lesions.

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TENASCIN SERUM LEVEL IS AN INDICATOR OF MALIGNANCY IN COLORECTAL NEOPLASIAS

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Tenascin (TN) is a glycoprotein of the extracellular matrix. In normal colon mucosa TN occurs in low concentrations. Inflammatory and neoplastic diseases show TN increase. We studied sera of patients with benign neoplasias (familial polyposis) and of patients with colorectal carcinoma by a double-sided-sandwich ELISA.

	n	TN (mean ± SD)
Normal controls	51	3.2 ± 1.7 μg/ml
Familial polyposis	17	3.9 ± 2.4 μg/ml
Colorectal carcinoma	241	6.8 ± 8.6 μ/ml

Though the total volume of neoplasic tissue in familial polyposis may be larger than in colorectal carcinomas, patients with familial polyposis have significant lower TN serum levels as patients with colorectal carcinomas ($P < 0.0001$ Mann Whitney U. test). TN serum level may be a parameter of malignancy. The clinical relevance of this result is subject of present investigation.

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DOSE-DEPENDENT 5-FLUOROURACIL CLEARANCE IN A CASE WITH DIHYDROPYRIDIMINE DEHYDROGENASE DEFICIENCY

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Deficiency of dihydropyrimidine dehydrogenase (DPD) impairs catabolism of 5-fluorouracil (5-FU) and thus can cause severe toxicity. Data on the 5-FU kinetics in these pts, however, are rare. In a female pt with severe toxic side effects as the cause for a premature of adjuvant levamisole/5-FU treatment for colorectal cancer, we conducted meticulous measurements of 5-FU kinetics when we had to resume 5-FU chemotherapy for hepatic metastases. We could demonstrate a dose-dependent impairment of 5-FU kinetics presumedly as consequence of a partial DPD deficiency. After a single bolus injection of 250 mg 5-FU we determined a half-life (t/2) of 8.5 min and an AUC of 2091 μM · min. After 500 mg 5-FU t/2 of 13.8 min was slightly above the upper limit determined in all other pts investigated so far. A further increase of 5-FU to 750 mg caused a dramatic increase of t/2 to 29 min and of the AUC to 10098 μM · min. To prevent toxic side effects we refrained from further increasing the 5-FU dose. Altogether, a threefold rise of 5-FU caused a 3.5 fold increase of t/2 and a sixfold increase of the AUC. Apparently, a major mechanism of impaired 5-FU catabolism in partial DPD deficiency is a DPD saturation at low 5-FU concentrations already. In this pt adjustment of the 5-FU dosage according to the impaired kinetics enabled a safe treatment without major side effects.

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TRIMETREXATE (TMTX) MODULATION OF 5-FLUOROURACIL/LEUCOVORIN (5-FU/LV) FOR ADVANCED COLORECTAL CANCER

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TMTX is a dihydrofolate reductase inhibitor which has been shown to potentiate FU cytotoxicity by increasing PRPP levels. Unlike methotrexate, TMTX does not compete with LV for cellular uptake and metabolism. In *in vitro* studies, TMTX enhances the cytotoxicity of FU/LV. Conti, *et al.* (*J Clin Oncol* 12:695; 1994) have reported a 20% PR rate in patients previously treated with 5-FU chemotherapy when TMTX was combined with FU/LV. In the current phase II trial, this regimen was evaluated in previously untreated patients with advanced colorectal cancer. TMTX, 110 mg/m^2 IV was administered 24 hours prior to leucovorin, 200 mg/m^2 IV and 5-FU, 500 mg/m^2 IV, followed by oral leucovorin, 15 mg q6hx7. Treatment was repeated weekly × 6 followed by 2 weeks rest. Accrual to this study has now been completed with 39 patients treated. Eleven are currently evaluable for response; objective responses have been achieved in 8 patients (78%) with 1 CR. The regimen has been generally well tolerated. Side effects include diarrhea and nausea/vomiting. This study will serve as the basis for a phase III trial of this regimen.

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SURVIVAL OF PATIENTS WITH LIVER METASTASES OF COLORECTAL ORIGIN TREATED WITH PERCUTANEOUS ETHANOL INJECTION (PEI) WITH OR WITHOUT SURGERY

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The purpose of the present study is to evaluate, after four years of observation, the influence of PEI upon the survival (S) of pts with liver metastases from colorectal carcinoma.

Between April 91 and December 94, 31 lesions (7 synchronous, 26 metachronous) with a mean diameter of 2.99 cm (0.8–6.1) in 24 pts (4F, 20 M, mean age 62.4 years, range 49–77) were treated with PEI.