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

G. Palmieri[1], P. Comella[1], R. Casaretti[1], A.P. Parziale[1], A. Daponte[1], A. Balasco[1], A. Gravina[1], G. Carteni[2], L. Manzione[3], G. Comella[1]
[1]National Tumor Institute, Naples, Italy
[2]Cardarelli Hospital, Naples, Italy
[3]Potenza Hospital, Italy

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

G.J. Poston, S.J. Walker, M.N. Hartley, R. Sutton
Department of Surgery, Royal Liverpool University Hospital, U.K.
University of Liverpool, Liverpool, U.K.

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

St. Riedl[1], M. Kadmon[1], U. Hinz[1], H. Bodenmüller[2], P. Möller[3], A. Faissner[4], Ch. Herfarth[1]
[1]Department of Surgery,
[2]Boehringer Mannheim, 82327 Tutzing, Germany
Departments of [3]Pathology, and [4]Neurobiology of the University of Heidelberg, 69120 Heidelberg, Germany

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

A. Schalhorn, M. Kühl, K. Heil, W. Wilmanns
Med Klinik III der LMU and Institut für Härmatologie der GSF, Munich, Germany

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

C. Blanke, B. Kasimis, P. Schein
Vanderbilt University, Nashville, TN, U.S.A.
VA Hospital, E. Orange, NJ, U.S.A.
US Bioscience, West Conshohocken, PA, U.S.A.

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.

749 POSTER

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

F. Silva, S. Perrone, A. Sala, G. Farina, A. Scanni
Medical Oncology, Fatebenefratelli, Oftalmico Hospital, Milan, Italy

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.

Using an ultrasound scanner (AU-590 Esaote-Biomedica), fine needles (Spinal-Icogamma, Ethanoject-TSK 22G), following the usual technique of alcoholization, varying amount of sterile alcohol (0.5–10 cc) at 95° were introduced into the lesions, for the total of 804 alcoholizations.

The response was evaluated by means of fine needle echo-guided biopsy (FNAB) carried out at the end of treatment: CR = necrobiosis and absence of CTM; PR = necrobiosis and rare, poorly-conserved, atypical CTM.

After the starting of PEI treatment (mean 4–9 months), 10 pts underwent surgery with exeresis of a total of 15 lesions. 21/24 pts responded to the treatment; of 33 treated lesions, we observed 6 CR (18.1%), 22 PR (66.6%), 3 NC and 2 local PRO. Histological confirmation of the cytologic response was obtained in 14/15 lesions undergone surgical exeresis. 10/24 pts died after a mean S of 13.5 months, in 9 cases due to extrahepatic disease progression.

Follow-up of the 14 alive pts is 17.5 months than S in 10 operated pts is 20.6 months, in 14 unoperated pts is 12.5 months. Overall survival is 15.8 months.

The comparison between our results and S reported in literature (6–12 months) comprehending any degree of hepatic involvement, is not possible since the criteria of admission are not homogeneous.

From a retrospective evaluation of 30 dead pts, followed in our service between '84 and '90 with liver metastases eligible for PEI but treated only with conventional CT, we observed a mean of S of 13.2 months; the mean follow up of our PEI-treated pts (17.5) has already surmounted that value, thus confirming the real efficacy of PEI.

The good result of mean follow-up is undoubtedly supported by the presence of pts undergone surgical exeresis. For this reason we calculated separately the mean S of unoperated pts, getting a result (13.2 months) next to the mean S of the survey group and expected to improve, since it regards still living pts.

In conclusion, we observed a real efficacy of PEI upon liver metastases, followed when possible by surgical exeresis; anyway PEI is a valid choice also in unoperable pts as palliative treatment in local control of disease.

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RANDOMIZED TRIAL OF INTRAOPERATIVE RADIOTHERAPY FOR COLORECTAL CANCER

V. Skoropad, B. Berdov, Yu. Mardynsky, L. Titova

Medical Radiological Research Center of Russian Academy of Medical Sciences, Obninsk, Russia

To evaluate the value of intraoperative radiotherapy (IORT) in colorectal cancer, a prospective randomized trial is carried out. For colon cancer, IORT plus surgery vs surgery alone is investigated. For rectal cancer, preoperative irradiation to the primary tumor was added to the treatment scheme in the experimental group. IORT was given in dose of 20 Gy, electron beam energy ranged from 8 to 15 MeV. After randomization and exclusion of unresectable and metastatic cases, the group consists of 42 patients. The mean age of patients was 56 years, 73% were males. Most part of the tumors presented B2 cases. There was no postoperative mortality. Approximately 1/2 of patients did not have postoperative complications. After a median follow-up period of 7 months (range 1–15) no patients in the experimental group had the disease recurrence. In the control group, 2 patients developed loco-regional failure.

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PALLIATIVE CYTOTOXIC THERAPY OF METASTATIC COLORECTAL CANCER IN GENERAL PRACTICE, A MODEL DESCRIBING THE COOPERATION BETWEEN THE MEDICAL ONCOLOGIST AND GENERAL PRACTITIONER

R. Smaaland[1], D. Skylstad[2]

[1]Department of Oncology, Haukeland Hospital, University of Bergen, N-5021 Bergen, Norway

[2]Nordås General Practice, N-5041 Nordås, Norway

Colorectal cancer is the most frequent diagnosed cancer in the western world. Less than 50% of the patients will today be cured of their disease. Thus, many patients will be in need of palliative treatment. The combination of 5-FU and Leucovorin has increased our ability to reduce tumour related symptoms by shrinking the tumour/metastases and not only mask them, e.g. with analgesics. However, it will not be feasible to administer such palliative oncologic treatment for this large patient group in the hospitals. In order to be able to offer this treatment to more patients, we have developed a program instructing general practitioners how to administer the drugs and how to evaluate the effect and side-effects of the treatment. The patients are first seen at the outpatient unit at the Department of Oncology. The patient's physician is then contacted by telephone and asked if he/she can administer the treatment according to a written guideline which will be sent. The patient is sent the necessary prescriptions for the drugs and equipment. 5-FU is administered as a bolus injection day 1 and 2, and Leucovorin is given 30 minutes later the same days (according to a Nordic recommendation). The treatment is repeated every 2 weeks. Since the start of this project in early 1994, 21 patients have been treated by general practitioners. Altogether 340 courses of therapy have been administered. Ninety percent of the doctors have reported a positive experience both with regard to patient care and the practical side of carrying through the treatment. On the basis of the practical simplicity of this treatment procedure and the positive reports of general practitioners, this model of cooperation is recommended in order to give more patients with advanced metastatic colorectal cancer the possibility of symptom reducing anticancer palliative chemotherapy.

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5-FLUOROURACIL (5-FU) PLUS LEUCOVORIN VERSUS 5-FU LEUCOVORIN PLUS INTERFERON-A GIVEN AS ADJUVANT CHEMOTHERAPY IN COLON CANCER

P. Papacostas, G.P. Stathopoulos, N.A. Malamos, E. Michailakis, S. Rigatos, B. Golematis

Hippokration Hospital Athens, Greece

In the present study adjuvant chemotherapy of two drug combinations was given in colon cancer patients.

Material and treatment: One hundred and five patients were included. 98 were evaluable. The patients were randomized in two groups, A and B. There were 48 men and 50 women, 67 with stage Duke's C and 31 B2. Primary tumor was excised and histology was adenocarcinomas. Group A patients were treated with 5-fluorouracil 400 mg/m^2 and Leucovorin 30 mg/m^2 daily for 5 days every 4 weeks for 6 months. Group B patients had the same treatment plus interferon-a 5 mU every 2d day for 6 months. Toxicity was common with mucositis and diarrhea and flu-like syndrome in Group B patients. *Results:* Median follow up was 38 months (6–58). Twenty-five patients recurred (25.5%). From group A the recurrence was 26.4% and from group B 24.4%. No statistical difference was observed. The median disease free survival was 14 months in either of the group. *Conclusions:* The combination of 5-Fu and leucovorin as adjuvant therapy in colon cancer seems to be effective and the addition of interferon-a did not reduce significantly the tumor recurrence.

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ISOLATED PELVIC PERFUSION FOR TREATMENT OF NON-RESECTABLE PELVIC RECURRENCES

M. Vaglini, M. Deraco, N. Santoro, L. Persiani, M.G. Inglese, V. Costagli, A. Chiti, M. Santinami, N. Cascinelli

National Cancer Institute, 20133 Milan, Italy

Twenty patients affected by non-resectable pelvic recurrence of primary pelvic malignant neoplasm were treated by Isolated Pelvic Perfusion. All patients were before treated by surgery and/or systemic chemotherapy and/or radiotherapy for their primary pelvic tumor. Patients underwent to laparotomy and IPP for 90 minutes at 40°C with high doses of drugs. Ten cases of rectal adenocarcinoma have been treated with Mitomycin-C (MM) and 5-FU and Mitoxantrane, in six cases of cervical carcinoma we employed a combination of MMC and Cis-Platin. One case of spindle cell anal carcinoma was treated with MMC, one case of penis carcinoma with Methotrexate, one case of endometrial adenocarcinoma with Cis-Platinum and finally one case of melanoma of the vulva with L-PAM. Three CR and seven PR were observed; three patients had a stable disease and two other patients were no responders and died for progression in few months. One patient is lost to follow-up and four patients recently treated are not evaluable. The advantage in responsiveness and the low incidence of complications suggest a possible indication of this technique as a first approach for pelvic recurrences.

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