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MTP-PE IN LIPOSOMES AS POST-OPERATIVE ADJUVANT THERAPY FOR COLON CANCER (DUKES' C): A PILOT ADJUVANT PHASE II TRIAL

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MTP-PE (muramyl-tripeptide-phosphatidyl-ethanolamine) in liposomes has been developed for the post-operative elimination of micrometastases. The drug induces tumoricidal monocyte/macrophages. At the time of starting this trial (early 1990) no established post-surgical adjuvant treatments for colorectal cancer were available. This pilot multicenter trial was initiated by randomizing patients to either 0.25 or 1 or 4 mg i.v. once weekly for 24 weeks with the aim to assess tolerability, immunomodulating activity and effectiveness of MTP-PE as prerequisite for a larger subsequent Phase III trial. Inclusion criteria were histological proof of Dukes' C adenocarcinoma curatively resected 10-21 days before randomization. Exclusion criteria were other chronic diseases.

Six patients received 0.25 mg, 12 patients 1 mg and 14 patients 4 mg. The 0.25 mg treatment arm was prematurely discontinued due to the occurrence of 3 early relapses at or before 6 months. As of February 1993 at median follow-up of 1.5 years relapses occurred in 5/6 in the 0.25 mg dose group, 2/12 in the 1 mg dose group and 3/14 in the 4 mg dose group. Treatment related adverse events were mainly fever and chills occurring in all 3 dose groups, most likely related to the elevated plasma levels of TNF and IL-6 which are signs of macrophage activation. Patients in the 4 mg dose group had significant leukocytosis 24 hours after the drug probably indicating a bone-marrow stimulatory effect of MTP-PE. This trial is now in further follow-up and latest data will be presented.

Keywords: colon cancer, adjuvant therapy, macrophage activation

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MONITORING TUMOUR RESPONSE TO 5-FLUOROURACIL IN COLORECTAL CANCER LIVER METASTASES USING POSITRON EMISSION TOMOGRAPHY AND F-18 DEOXYGLUCOSE. Ellis P, Findlay M, Hanrahan A, Flower M, Cronin B, Pratt B, McCready R, Ott R, Cunningham D. The Royal Marsden Hospital and Institute of Cancer Research, Sutton, Surrey, UK

This study is designed to test the value of measuring pretreatment and early on-treatment tumour metabolism using positron emission tomography (PET) and F18-deoxyglucose (FDG) in predicting the response of colorectal cancer liver metastases to continuous infusion 5-fluorouracil (5FU) +/- interferon-α.FDG-PET scans were performed with patients fasted; pre-treatment; 1-2 weeks and 4-5 weeks on treatment. A single image was acquired using the MUP-PET large area positron camera, 45-75 minutes post IV injection of FDG (45-90 MBq). Tumour to normal liver (T:L) ratios and tumour standardised uptake values (SUV) were calculated from the region of interest analysis of the FDG images. Tumour response was evaluated at 12 weeks using CT scans and 6 weekly using tumour markers. To date 15 patients have been studied, 3 being withdrawn due to protocol violation (non-fasting scan; no CT evaluation). 12 patients have a total of 16 liver metastases evaluable. Differential tumour responses within the same patient were seen. Pre-treatment FDG SUV's or T:L ratios did not predict tumour response to 5FU. Both the reduction of tumour FDG SUV's at 1-2 and 4-5 weeks and the reduction in FDG T:L ratios at 4-5 weeks of 5FU treatment correlated with subsequent tumour response. Neither the reduction in tumour SUV's or T:L ratios correlated with tumour marker responses. These preliminary results suggest a role for FDG-PET in predicting tumour response to treatment in colorectal cancer liver metastases possibly as early as 1-2 weeks on treatment. Correlation of tumour marker response with FDG-PET is poor presumably because of differential production by metastases.

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DOUBLE ALTERNATE MODULATION OF HIGH DOSE FLUOROURACIL (5FU) BY INTERFERON ALPHA (IFNα) AND PHOSPHONACETYL-L-ASPARTIC ACID (PALA) IN PATIENTS WITH ADVANCED COLORECTAL CANCER (ACC), A MULTICENTER PHASE II STUDY.

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We postulated that 5FU resistance might be decreased by alternate modulation of 5FU. Our ambulatory treatment schedule consisted of 5FU 60 mg/kg/48h continuous i.v. combined during uneven cycles with two s.c. injections of IFNα-2b (Schering Plough, Amstelveen) 10 MU/dose, prior to and halfway 5FU infusion, and during even cycles with PALA (US BioScience, Watford) 250 mg/m^2 i.v., 24h before 5FU infusion. Cycles were given weekly for 4 weeks, and once every 2 weeks thereafter. We treated 21 patients (pts) with ACC, previously untreated except 1, median WHO performance 1 (range 0-2), age 61 yrs (23-73), serum LDH 375 U/l (217-2310), and WBC 9.3x10^9/l (5.2-20.5). Response rate (RR) was 5% (1 PR, 6$^+$ months, 95% confidence interval 0-15%). No grade III/IV (WHO) toxicity occurred in 171 cycles. These results compare unfavourably with the outcome of our two previous studies in which the same 5FU dose and schedule was used together with leucovorin (RR 26%), and with IFNα+leucovorin (RR 26%). We conclude that this schedule of alternate modulation of 5FU is ineffective in pts with ACC. The fact that only pts with disease progression in the 2 months prior to entry and/or with symptomatic disease were included might have negatively influenced the outcome.

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FLUOROURACILO(FU) VERSUS COMBINATION OF FU WITH HIGHER OR LOW DOSE OF LEUCOVORIN(LV) AND PLUS OR MINUS INTERFERON (IFN) IN ADVANCED COLO-RECTAL CANCER.-

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We conducted a clinical trial to determine whether the combination of FU with high or low dose of LV plus or minus IFN are superior to FU alone. 163 evaluable patients (pts.) with Advanced Colorectal Cancer, median age 58 years (range 33-76),median PS of 80, (range 70-100) were treated in first line chemotherapy with FU or FU and high or low dose of LV plus or minus (IFN), characteristics of treatment, number of Pts. and response were:

TREATMENT	pts.	CR%	PR%	ED%	RR%
FU	26	-	30	10	40
FU/IFN	47	-	40	-	40
FU,LV (200 mg)	22	4.6	33	4,6	42
FU,LV(200mg)IFN(5 MU)	21	-	33	8	41
FU,LV (20 mg)	21	-	43	-	43
FU,LV (20mg)IFN (5MU)	26	7	41	-	48

The combination of FU with high dose of LV caused severe stomatitis and diarrea,but FU with low dose of LV plus or minus IFN has had moderate toxicity and a good RR superior to FU alone and the other regimen.

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A PILOT STUDY OF INTRAARTERIAL CHEMOTHERAPY (IAC) IN METASTATIC COLORECTAL CARCINOMA (CC)

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Between January 1990 and October 1992, 17 evaluable patients (pts) (9 males, 8 females), median age 58 (42-73) median PS 1(0-3),with liver metastasis from CC, received IAC as follows: cisplatin 20mg/m^2 over 12hrs; 5 fluorouracil 700mg/m^2 over 12 hrs with leucovorin 120mg/m^2; all drugs were given daily x 5 days, Q5 weeks. Ten of the 17 pts had received systemic chemotherapy. Eight (47%) responded to IAC, including 2 (12%) with CR and 6(35%) with PR. Response rate was 50% in previously treated pts (5/10) and 43% in pts without prior therapy (3/7). Median survival was 10ms for all pts, 21ms for responders. Hematological toxicity was mild with 5 of a total of 92 IAC courses resulting in GrIII-IV toxicity, including 3 episodes of leukopenia and fever; 4 pts developed GIII-IV diarrhea. Two pts had hepatic artery thrombosis and one had sclerosing cholangitis. IAC to the liver as given here to pts with CC results in a substantial response rate with improved quality of life in responders.

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5FLUOROURACIL (5FU) WITH LOW DOSE LEUCOVORIN (LCV) IN ADVANCED COLORECTAL CARCINOMA (CC)

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NINETY SIX EVALUABLE PTS. 50 MALES, 46 FEMALES, MEDIAN AGE 68(18-88) MEDIAN PS 1(0-3), WITH METASTATIC CC WERE GIVEN IV CHEMOTHERAPY WITH 5FU AND LOW DOSE LCV AS FOLLOWS: 5FU 370mg/m^2 I.V. PUSH DAILY FOR 5 DAYS, IMMEDIATELY PRECEDED BY LEUCOVORIN 20mg/m^2 I.V. PUSH, q. 28 d. METASTATIC SITES INCLUDED: LIVER 60PTS., LUNGS 18 PTS. AND INTRAABDOMINAL MASSES 17 PTS. 18 PTS. (19%) ACHIEVED AN OBJECTIVE RESPONSE (>50% REDUCTION OF KNOWN MEASUREMENTS). 2 PTS. HAD IMPROVEMENT LESS THAN 50% AND IN 29 PTS. (30%) STABILIZATION OF DISEASE WAS OBSERVED. 56% OF THE PTS. WHO WERE SYMPTOMATIC BEFORE INITIATIN OF TREATMENT HAD SYMPTOMATIC RELIEF WITH 5FU-LCV. MEDIAN DURATION OF RESPONSE WAS 8 MONTHS AND THE MEDIAN SURVIVAL (MS) OF RESPONDERS REACHED 16 MONTHS (7-19). MS FOR ALL 96 PTS. WAS 13 MONTHS (2-25). TREATMENT WAS WELL TOLERATED. ALTHOUGH OBJECTIVE RESPONSES TO 5FU-LCV OCCURED IN ONLY ABOUT 1/5 OF ALL PTS. SUBJECTIVE SYMPTOMATIC IMPROVEMENT WAS FREQUENTLY OBSERVED.