13.

SEQUENTIAL METHOTREXATE(MTX) AND 5-FLUOROURACIL(FU) IN METASTATIC COLORECTAL CANCER(CRC). RESULTS OF A PHASE II STUDY.
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Experimental studies have shown synergism of MTX and FU if MTX preceds FU. Following evaluation of a regimen in phase I and II pilot studies a multicenter trial was initiated in metastatic CRC. Eligibility criteria included: measurable lesion, no prior chemotherapy, symptomatic or progressive disease, normal bone marrow and kidney function, ECOG performance status(PS) 3 or better, absence of effusions. Treatment consisted of MTX 150mg/m² iv push followed by MTX 150mg/m² iv over 4 hrs, FU 900mg/m² iv push 7 hrs after MTX and leucovorin 22.5mg po q 6 hrs for 8 doses starting 24 hrs after MTX. Urinary pH was kept >7. This was repeated every 2 weeks x3, then every 3 weeks until progression. 42 patients are evaluable for response. Median age was 57 yrs(32-74). Median time from first diagnosis to chemotherapy was 15.5 mo(0.5-38).Mean ECOG PS was 1.05. Response was determined according to WHO recommendations. Complete response was seen in 1 patient with pulmonary metastases for 14 mo. Partial response was achieved in 15 pts for a median of 7.5 mo with an objective remission rate of 38%. 17 pts had stable disease for a median of 7 mo. Median survival of all evaluable pts was 12.5 mo. Toxicity was mild and consisted mainly of mucositis, slight nausea and bone marrow depression. It is concluded that this schedule of sequential MTX and FU is well tolerated and effective in metastatic CRC. Presently this regimen is being compared to single agent FU in a randomized phase III trial. Although for human cancer the optimum dosages and interval are unknown, review of the literature suggests a time interval of 4 or more hours to be superior to a 1 hour interval.

14.

EXPERIMENTAL CHEMOTHERAPY USING HUMAN COLORECTAL XENOGRAFTS.
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Male C3H mice were conditioned for 4 days with an immunosuppressive protocol including procarbazine, cyclophosphamide and antilymphocyte serum. Fragments of human colorectal tumors were then grafted subcutaneously. After two weeks, groups of mice carrying the xenografts were treated with single, maximally tolerated doses of 5-fluorouracil (5-FU), dimethylmyleran (DMM), x-rays, cis platin, adriamycin, BCNU, cytosine arabinoside, bleomycin, etoposide, melphalan, vinblastine, mitomycin C and procarbazine. 5-FU, DMM and x-rays were also given at lethal dosages followed by bone marrow rescue. The changes in tumor volume as compared to the controls were assessed up to day 30.

From the results obtained with 4 colorectal tumors, the following conclusions can be made. 1) Superdosis chemotherapy with 5-FU, DMM or x-rays (all combined with bone marrow) is more effective than treatment with maximally tolerated doses. 2) Tumors may show selective chemotherapeutic sensitivity. For instance, one colorectal carcinoma responded markedly to BCNU while three other carcinomas were resistant. Thus, 3) predictive testing of human xenografts should allow to select the most effective chemotherapeutic agent for the individual clinical tumor.

15.

INTRAARTERIAL INFUSION FOR COLORECTAL LIVER METASTASES.
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Selective hepatic artery infusion was pioneered by Wat as early as 1964. The arterial catheter was positioned dur a laparotomy after surgical staging of the tumour. In 1982 Niederhuber emphasized the necessity of an optimal positioning of the catheter and the use of a totally implanted pump. FUDR was already used in 1964 and is still now the m commonly used drug. Ensminger's pharmacological studies confirmed in 1983 that FUDRis really the best drug to use hepatic metastases of adenocarcinomas since it has the hig first pass extraction by the liver and one high total body clearance. Other drugs include Mitomycin-C, cisplatinium, dichloromethotrexate and Adriamycin, alone or in combinati but so far their use did not add much to the previous scor Criteria of remission differ so much and lack of homogenei of clinical material is such that strict comparison is non sense. General consensus is limited to the point that remi sion rate is higher with continuous arterial infusion than with discontinuous i-v. therapy. Fortunately Sugarbaker pr posed in 1984 an international classification, the use of which will make things clearer and eventually permit to compare results of different series. Toxicity was also ins ficiently studied until recently (Ensminger, Balch, Kemeny Toxicity can be acute or subacute (gastroduodenal) or chro (sclerosing cholangitis) and differs considerably from con nuous i-v. toxicity (acute or subacute colitis). Stumbling block remains yet extrahepatic sites of metastases, their prevention and treatment, possibly multiple catheter pumps U.S. controlled trials started in 1983 will soon clarify t situation.

16.

POLARIZATION AND LOCOMOTOR RESPONSES OF WALKER 256 CARCINOSARCOMA CELLS: STIMULATION BY MICROTUBULE-DISASSEMBLING AGENTS AND INHIBITION BY PHORBOL MYRISTATE ACETATE (PMA).
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The spontaneous motile behaviour of tumor cells and its regulation by chemokinetic stimuli may be an important factor controlling invasiveness. We have studied the locomotor behaviour of Walker carcinosarcoma cells and its chemokinetic modulation. The microtubule-disassembling drugs colchicine (10^{-7}M to 10^{-5}M), vinblastine (10^{-8}M to 10^{-5}M) and nocodazole (10^{-5}M) were found to stimulate polarization of Walker carcinosarcoma cells. Taxol, a drug which stabilizes microtubules, suppressed spontaneous polarization. These results indicate that polarization of Walker carcinosarcoma cells is influenced by microtubules. Cytochalasin B completely inhibited spontaneous and stimulated polarization, indicating that it is microfilament-dependent. Polarization responses were associated with stimulated locomotion. The increase in the mean speed of the cell population was due to an increase in the proportion of migrating cells and the speed of the migrating subset. PMA inhibited spontaneous polarization as well as the type of polarization elicited by the microtubule-disassembling agents colchicine, vinblastine and nocodazole. Suppression of cell polarization was associated with inhibition of locomotion. The ID_{50} was in the range between 10^{-9} and 10^{-8}M PMA. At 10^{-6}M PMA, polarization and locomotion were almost completely suppressed. The mechanisms by which PMA suppresses motility will be discussed. Supported by the Bernese and the Swiss Cancer League.