Symposium no. 7: Tumour Drug Delivery

7.007

31P MRS STUDY ON EXPERIMENTAL MELANOMA TUMOURS TREATED WITH DTIC

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We used in vivo 31P MRS (4.7 T) to detect metabolic alterations occurring in human melanoma tumours implanted in nude mice, during inhibition of tumour growth induced by Dacabazine (DTIC). The following spectral differences were exhibited by DTIC-treated with respect to control tumours, on day 1 after the DTIC injection , prior to occurrence of any significant change in tumour size: up-field shift of inorganic phosphate (Pi), corresponding to intratumoral acidification of 0.2-0.4 pH units, associated with a relative increase in the Pi signal area with respect to the total 31P resonance profile. DTIC, the most extensively studied agent against malignant melanoma, is known to block the cell cycle in the "S" phase. Flow cytometry analyses, performed on the same system analysed by MRS, allowed us to confirm an increase of cell population in the "S" phase and a decrease in "G.." phase, on day 1 after DTIC treatment. Previous 31P MR studies on synchronized HeLa cells [1] allowed us to dectect a significant correlation between intracellular pH and cell cycle phases, with a difference of about 0.4 units between mid S and late G1. The alterations observed in melanoma tumours treated with DTIC are consistent with an intracellular acidification during the S phase . [1] Podo, F. et al., 7th SMRM Meeting, p.214, 1988. We thank AIRC and EC Concerted Action COMAC-BME II.1.3 for financial support.

7.008

CLONAL GROWTH OF HUMAN OVARIAN CANCER CELL LINES IS ENHANCED BY GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM-CSF). G. Cimoli, P. Russo, G. Billi, G.L. Mariani, R. Rosso, A. Ardizzoni and M. Venturini. IST - Genova, Italy.

Human granulocyte-macrophage colony stimulating factor (GM-CSF) is a regulatory glycoprotein that stimulates the production of granulocytes and macrophages from committed hematopoietic progenitor cells both "in vitro" and "in vivo". In this report, we show that recombinant human GM-CSF enhances colony formation by nonhematopoietic human ovarian cancer cell lines, IGROV-1, A2774, ME-180, Pa-1 and A2780. GM-CSF enhances, also, the colony formation by cells obtained from fresh ascites of two patients affected with ovarian mucinous cystadenocarcinoma and serous papillary ovarian carcinoma respectively. Our observation has been made with GM-CSF ranges varying between 0.1 to 1 ng/ml; these concentrations are equivalent to the dosages generally used for bone marrow recovery after chemotherapy. From a clinical point ov view, it would be important to consider the possible responsiveness of nonhematopoietic tumor cells to GM-CSF. (AIRC "CSF", 1991).

7.009

PRECLINICAL EVALUATION OF POLYMER-BOUND DOXORUBICIN

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N-(2-Hydroxypropyl)methacrylamide (HPMA) copolymers were synthesised to contain doxorubicin (DOX) attached via lysosomally degradable Gly-Phe-Leu-Gly spacers. When administered to mice bearing i.p. L1210 at doses 2.5 - 50mg DOX/kg the highest T/C seen for conjugates was >762 compared with T/C of 214 for free DOX. In addition conjugate administration at 30mg/kg resulted in a large number of long term survivors (17/20). HPMA copolymers containing DOX were also shown to be active against a number of solid tumour models; M5076, Walker sarcoma and the xenograft LS174T. In each case the conjugate produced an increase in survival greater than seen with free DOX and in certain cases this was accompanied by complete tumour regression. HPMA-copolymer DOX exhibits a wide range of antitumour activity and its mechanism of action is dependent on; lysosomal activation of the macromolecular prodrug, alteration in DOX pharmacokinetics resulting in tumour specific accumulation and a marked reduction in all aspects of DOX-related toxicity.

7.010

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Antitumor effects of alkyl phosphocholines in different murine tumor models; use of liposomal preparations.

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Hexadecylphosphocholine and its analogues with a longer alkyl chain (C_{18} and C_{20}) were examined for their antineoplastic activity in the murine tumor models P 388 leukemia, B 16 melanoma, the mammary carcinomas C3H and Ca 755 and in the human MT-1 mammary tumor in vivo.

The maximum tolerated doses were determined and found to be higher in mice than in rats. The toxicity of the alkyl phosphocholines increases with chain length.

The murine mammary carcinoma C3H and the human MT-1 mammary carcinoma showed response to hexadecylphosphocholine whereas the classical screening models were not responsible to the synthetic lipids. Furthermore, it was possible to show activity in a mitoxantrone-resistant P 388 leukemia. Examination of the activity of possible cleaving products of HPC gave no information about the possible mechanism of action of the used etherlipids. Liposomes with encapsulated mitoxantrone and formed from alkyl phosphocholines, cholesterol and dicetylphosphat had the same activity against P 388 mouse leukemia as the free drug.

The hemolytic activity of the three lipids was tested in vivo and assumed to be related to toxic deaths of single animals observed sometimes independent of schedule and dose.

7.011

SYNTHESIS AND STUDY OF TYROSINE NITROSOUREAS AS POTENTIAL ANTICANCER AGENTS.

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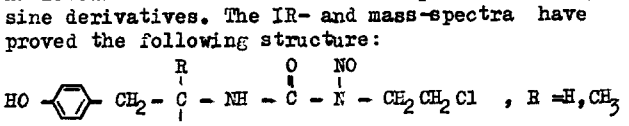
Bearing in mind that: 1)the tyrosine is a precursor in the melanin biosynthesis and 2)it concentrates mainly in pigment melanomas, we have synthesized nitrosoureas in which the carrier portions are tyrosine derivatives. The IR- and mass-spectra have proved the following structure:



The alkylating, carbamoylating activities and chemical half-life were determined. The influence on the DOPA-oxydase activity of mushroom tyrosinase by the tyrosine nitrosoureas was studied and compared with the antimelanoma drug CCNU.

The tyrosine nitrosoureas have shown an inhibiting effect on tyrosinase. We consider that the high inhibiting effect is due to both the carbamoylating activity of the nitrosoureas, and their action as competitive inhibitor, as well.

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7.012

ANTIPYRINE METABOLISM DURING CHEMOTHERAPY IN CANCER PATIENTS.

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The data about the influence of anticancer drugs on mixed hepatic oxigenase system (MHEOS) are still few and incomplete. We used antipyrine test to investigate the influence of 5-Fluorouracil (5-FU) plus high dose folinic acid(HDFA) on MHEOS activity in 18 subjets with massive liver involvement from primary colon cancer. There were 9 male and 9 female, the median age was 55 years (range 42-73). No previous chemotherapy was allowed. The antipyrine test (18 mg/kg orally) was performed just before, after the first cycle of chemotherapy (Folinic acid 200 mg/m_2/day plus 5-fluorouracil 370 mg/m_2/day x 5 days). In order to evaluate the influence of the tumour burden on the liver metabolic efficiency (no change, regression or progression) the antipyrine test was repeated after 4 cycles of chemotherapy. Results: basal antipyrine clearance (AP cl) 0.422 ml/min/kg ± 0.03, half-life(T/2)16.4 h ± 1.1h. After the first cycle AP cl 0.437 ml/min/kg ± 0.03, T/2 16.1 ± 1.2 h. After 4 cycles AP cl 0.458 ml/min/kg ±0.04, T/2 17.0 ± 1.2 (ns). No difference was observed between "responders" and "non responders" patients. Even when largely involved by neoplastic disease the hepatic drug metabolizing system is still valid. 5-FU does not influence the MHEOS activity in man.