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7.037

BIODISTRIBUTION AND IMMUNE EFFECTS OF LIPOSOME ENCAPSULATED INTERLEUKIN-2 (IL-2).

H.K.B. Silver, R.K.H. Wee, S. Kong, M. Bally, T. Madden. Department of Advanced Therapeutics, British Columbia Cancer Agency, Vancouver, Canada.

To examine the potential therapeutic advantage of liposome encapsulated IL-2, the biodistribution and biological activity (macrophage and lymphokine activated killer (LAK) cell activation) of intravenously administered small (0.1 μm) and large (1.0 μm) egg phosphatidylcholine/cholesterol liposomal IL-2 formulations were studied in mice. Macrophage superoxide production was greatest following administration of free IL-2. *In vivo* LAK activation indicated equivalent activity for free or liposomal IL-2. Small liposomes exhibited longer circulation lifetimes compared to large vesicles and accumulated to the greatest extent in lymph nodes. Therefore, encapsulated IL-2 may provide therapeutic advantage by permitting prolonged exposure with some preferential distribution to immune organs. Further formulation and animal tumour model studies are in progress.

7.038

Improved antitumor effect and increased side effects at combined hepatic arterial treatment with degradable starch microspheres and adriamycin or the nitrosoureas TCNU and BCNU in rats with a liver adenocarcinoma.

U Stenram, B Jakobsson, G Roos, H Teder, I El Hag. Departm Pathol, Lund University, S-221 85 Lund, Sweden.

Arterial administration of degradable starch microspheres (DSM) reduces the blood flow, resulting in prolonged exposure of the target to concurrently injected drugs and in hypoxia. The model was tested in rats with a liver adenocarcinoma.

Experiment A chemically induced adenocarcinoma of the colon was inoculated into the liver in rats. 9 or 10 days later, tumor size was measured and the rats were given either 5 mg TCNU or 5 mg BCNU or 4 mg adriamycin (adr) /kg body weight with or without 60 mg DSM/kg b w for 60-90 s, or DSM or saline alone. In additional experiments, the adr+DSM treatment was combined with norepinephrine in three protocols. The rats were killed 7 days later.

Results DSM alone had no effects. DSM increased the antitumor effect of adr, TCNU and BCNU. In several rats, large liver necroses appeared at the combined treatment but not with the drugs or DSM alone. Adr+DSM gave a body weight loss.

Addition of nor-epinephrine in doses of 20 μg/kg b w/min 3 min before, during and 1 min after the adr+DSM treatment significantly reduced body weight loss. A simultaneous decrease in antitumor effect and liver necroses was not significant. We observed gastric necroses in 3 of 8 and 1 of 8 rats given adr+DSM but none at addition of norepinephrine in two protocols.

Conclusion DSM increases the antitumor effect of several cytostatic drugs, but side effects may appear. These can be partly prevented by norepinephrine.

7.039

CYCLOPHOSPHAMIDE (CPM) LIPOSOME-DRUG COMPLEXES

D. Todorov, K. Maneva, S. Michailova, G. Ganchev, P. Vasilev, V. Kapourdov, K. Katerinsky

National Oncological Center, Medical Academy, Sofia 1156, Bulgaria

CPM was included in liposome drug complexes that were obtained by the ultrasonic method and by the controlled detergent dialysis with the help of "Liposomat" (Dianorm - Germany). With the *in vitro-in vivo* method, the so-called bio-assay of the surviving tumor cell fraction, a direct increased cytotoxic effect of liposome CPM suspension included was determined on cells from leukemias L1210, P388 and Lewis lung carcinoma (LLC). The liposomal structure was proved by ultrastructure detection on cultivated LLC tumor cells *in vitro*.

7.040

W.Tomkowski, M.Szturmowicz, A.Fijałkowska, S.Filipecki.

Intrapericardial cisplatin in malignant pericardial effusion.

9 patients with malignant pericardial effusion of various neoplastic etiology (mean age 55,3 years) were studied. After insertion of polyurethane catheter (Cavafix), fluid was drained and cisplatin (10 mg in 20 ml of normal saline) was instilled over 5 minutes on 5 consecutive days (total cisplatin dose-50 mg). If fluid reacumulation ocured, the courses were repeated every 2 or 3 weeks. In all patients (in 2 after 20 mg and 30 mg of cisplatin, in 6 after one course, in 1 after four courses) complete therapeutic response (no more fluid reacumulation) was obtained. No local, hematologic or renal complications of cisplatin -therapy were observed. We believe, that in patients with malignant pericardial effusion of various neoplasmatic etiology, the intrapericardial administration of cisplatin is effective and save.

7.041

THE ANTI EGFR MINT5 MAB IS ABLE TO SPECIFICALLY TARGET RIP α-SARCIN CYTOTOXICITY AGAINST RELEVANT TARGET CELLS

E. Tosi[1], S. Canevari[1], P. Alberti[1], M. Gadina[1], S. Muñoz[1], S.M. Salvarelli[2] and M.I. Colnaghi[1]. [1]Oncologia Sperimentale E, Istituto Nazionale Tumori, Milano, Italy. [2]Seccíon de Inmunoquímica, Dpto. Investigacíon, Hospital "Ramón y Cajal", Madrid, Spain.

The potential usefulness in cancer therapy of the MINT5 MAb, which recognizes the EGFR extracellular domain and competes with the natural ligand, has been evaluated. The cytotoxic effects of the antibody were tested in vitro on malignant human cell lines with EGFR ranging from 0 to $2x10^6$ receptors/cell and on human fibroblasts and lymphocytes. The capability of MINT5 to inhibit the cell proliferation significantly correlated with the number of EGFR on the plasma membrane, whereas no effect was observed on protein synthesis. Upon conjugation with RIP α-sarcin, the immunotoxin only inhibited the protein synthesis of lines overexpressing EGFR. Moreover, on all the lines tested, the concentration of the MINT5-α-sarcin conjugate required to inhibit to the same extent the cell growth, was on average 1000 times lower than the concentration of the MAb alone. The IC_{50} of the immunotoxin on A431 cells ($1.4x10^6$ EGFR/cell) was about $4x10^{-12}$M.

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7.042

CYTOTOXICITY OF CHLORAMBUCIL (Chl), 5-dFU-DEOXY-FLUORURIDINE (5dFU) AND THEIR FATTY ACIDS CONJUGATES AGAINST HUMAN LYMPHOMA AND COLON CARCINOMA CELLS.

José URIEL, Thérèse HALMOS, Juan TORRES, Patricia MORONI and Kostas ANTONAKIS

Institut de Recherches Scientifiques sur le Cancer. BP N° 8, 94801-VILLEJUIF (France).

The cytotoxic activity of Chl, 5dFU and their conjugates with oleic (18:1), arachidonic (20:4) and docosahexenoic (22:6) acids has been assayed in vitro upon a human lymphoma cell line (Raji), a human colonic carcinoma cell line (HT-29) and, comparatively upon normal human lymphocytes. The cell cytotoxicity of conjugates Chl-20:4, Chl-22:6, 5dFU-18:1 and 5dFU-22:6 was higher than the individual toxic potential of either Chl, 5dFU or fatty acids, as well as of mixtures of conventional drugs and fatty acids. The same conjugates were toxic against PHA-activated lymphocytes but lacked of toxicity against quiescent, non-activated ones. In conclusion, the coupling of unsaturated fatty acids with Chl or 5dFU increases: a/the selectivity against neoplastic versus quiescent lymphocytes and b/ the toxicity of the drugs alone. The selective effect of drug-fatty acids conjugates towards proliferating cells is discussed in relation with the activation of an autocrine alphafetoprotein/ receptor pathway in malignant cells and in mitogen-activated lymphocytes.