Symposium no. 7: Tumour Drug Delivery

7.013

HUMAN-ANTI-MOUSE-IMMUNOGLOBULIN RESPONSE IN THE COURSE OF ADJUVANT MONOCLONAL ANTIBODY TREATMENT WITH 17-1A IN PATIENTS WITH COLON CARCINOMA. R.Gruber, C. Reiter, D. Flieger, W. Höchtlen-Vollmar and G. Riethmüller. Institut für Immunologie München.

In a randomized phase II clinical study, 80 patients with colo-rectal carcinoma of stage Dukes C were treated with the monoclonal antibody (MAb) 17-1A after curative surgery. The regimen consisted of a single infusion of 500mg 17-1A within two weeks after surgery, followed by 100mg of MAb four times every four weeks. Sera were taken every two to three weeks and screened for human-anti-mouse-antibodies (HAMA's). HAMA's were detected by a sandwich-ELISA. The ELISA-mikrotiterplates were coated with MAb 17-1A, diluted paticnts sera were added and detected by 17-1A-bio and avidin-peroxidase. No HAMA's could be detected with this assay in 20 sera of control patients and in all patients sera before treatment. For statistical analysis the patients were divided into two groups, "responders", who were healthy at the end of observation time, and "non-responders", who relapsed or died during observation time. In both groups about 30% of patients did not develop HAMA's. The highest HAMA-titers appeared at week 18, 19 and 24. The mean-titer for the responder group were markedly higher at week 18 and 19 than the mean-titer for the "non-responders". Further studies are needed to answer the question whether this difference is due to an impaired immune reactivity in patients with a higher tumor burden, or whether higher HAMA-titers are beneficial for the anti tumor effects of monoclonal antibody treatment.

7.014

DESIGN OF BRANCHED POLYPEPTIDE-ANTICANCER AGENT CONJUGATES FOR DELIVERY

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Synthetic polymeric polypeptides are of interest as macromolecular carriers for delivery of anti-cancer agents. In the present study a comparison was made of conjugates containing methotrexate (MTX) or daunomycin (Dau) covalently attached to branched polypeptides composed of a poly(L-Lys) backbone and oligomeric side chains of various, amino acid composition and/or sequence. Dau was coupled using its cis-aconityl derivative, while MTX was attached with ECDI. The conformation of the conjugates were studied by CD spectroscopy. Conjugates were tested for ability to alter the cytotoxicity of the relevant free drug against osteogenic sarcoma cell line 791T/36 Biodistribution profile of labelled conjugates were analyzed in Balb/c mice. It was attempted to find correlation between the observed delivery parameters of conjugates and the charge characteristics of the carrier, method of coupling and conformation of the conjugates.

7.015

A novel watersoluble nitrosourea - PONU, antitumour activity against intracerebral or intraperitoneal lymphoid leukaemia L1210

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PONU [1-(2-chloroethyl)-3-dimethylphosphinyl-methylene-1-nitrosourea] is a novel well watersoluble, phosphorous-containing nitrosourea derivative. The antitumour activity of PONU in BDF_1 mice bearing intracerebral (i.c.) (1.10^4 tumour cells/mouse) or intraperitoneal (i.p.) (1.10^5 tumour cells/mouse) lymphoid leukaemia L1210 was studied comparatively. PONU possessed a high antitumour activity in i.p. L1210 (T/C.100 = 697.7%) and 100% "cured" animals and low activity on i.c. L1210 (T/C.100 = 139.6%). The obtained data were discussed about the relation between water- or lipidsolubility of the drug molecule and its possibility to pass biological membranes and hemato-encephalic barrier.

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7.016

FIXED DOSE ADJUVANT CHEMO WITH/WITHOUT TAMOXIFEN IN STAGE II CANCER OF THE BREAST

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The following protocal has been used for 11 years in pts. with stage II breast cancer.
Cytoxan 500mg IV day 1 and day 8.
Vincristine 1mg day 1 and day 8.
5FU 500mg IV day 1 only.
Methotrexate 50mg day 8 only.
ER/PR positive= CMFV for 6 months then 2yrs of Tamoxifen 10mg BID.
ER positive/PR negative= CMFV for 1yr and Tamoxifen 10mg BID for 2 years.
ER/PR negative= CMFV for 1 year.
ER negative/PR positive= CMFV for 6 months.
Total patients treated= 60. 45 post menopause; 15 pre menopause; 2 of which were non compliant.
Relapse, pre menopausal: 4 of 13 in 3 years. 3 are PR negative and 1 PR positive.
Relapse, post menopausal: 8 of 45 relapsed. 5 of the 8 died from breast cancer. 3 are alive 2 1/2 yrs post relapse. 6 of 8 were PR neg.
Median follow= 60+ months with 12 of 60 pts. relapsed. Thus 80% of the patients are disease free.

7.017

Effect of methotrexate on protein composition of hamster hepatoma cellular fractions

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We have recently shown that methotrexate (MTX), known drug useful in human oncology, inhibited hamster Kirkman-Robbins hepatoma growth of about 89.2±3.5%. To analyze the effect of this cytostatic agent on protein composition of different hepatoma cellular fractions, i.e., nuclear, mitochondrial (10P), microsomal (100P) and cytosolic (100S) one- and two-dimensional gel electrophoresis followed by silver and Coomassie Blue staining was performed. The biosynthesis and/or metabolism of several components especially in mol.wt range of about 29 000-37 000, 80 000--100 000 and 140 000-190 000 in examined cellular fractions was found to be affected by MTX treatment.

7.018

INTRAARTERIAL CHEMOTHERAPY, SENSITIZING RADIATION AND LOCOREGIONAL HYPERTHERMIA IN THE TREATMENT OF LIVER METASTASES

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Between 8/1989 and 1/1991 a total of 32 pats. with breast cancer and liver metastases have been treated with intraarterial chemotherapy, low-dose radiation and local hyperthermia. Via the femoral artery an angiographic catheter was placed into the hepatic artery. 90 mg/sqm Epirubicine were given within 2 hours followed by 900 mg/sqm 5-FU over 24 hours. Additionally the liver was exposed to low-dose irradiation (600 rads) and 434 MHz microwave hyperthermia. So far 86 treatment courses have been performed. 75 % of pats. showed CR or PR. Side effects: epigastric pain 16 %, nausea 30 %, leucopenia 31 %, one treatment-related death. Long-term results will be presented.