VBR 26

CYTOTOXICITY OF BLEOMYCIN AND PEPLOMYCIN ON HUMAN TUMOR CELLS IN VITRO.

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Human clonogenic tumor cells from various human tumors were cultured in a methylcellulose monolayer assay. Single cells were seeded in Iscove's modified Dulbecco's medium, fetal calf serum and methylcellulose. Bleomycin and Peplomycin were added at concentrations between 10^{-2} and 10 ug/ml. Incubation was performed at 37°C in 7,5 % CO_2. After 8-10 days of incubation, colonies could be scored under an inverted microscope. Each tumor showed individual dose response curves. In two out of four malignant melanoma probes, Peplomycin showed a considerable stronger cytotoxicity than Bleomycin; in one case the difference was less pronounced and in one case the dose response curves were identic. In two out of four samples from myosarcomas, Peplomycin proved to be more cytotoxic than Bleomycin, in two probes the dose response curves showed identic effects. In two samples from colon carcinomas Bleomycin showed at reduction of colony formation 10 ug/ml to 40-50% and 60-65% of control, whereas the incubation with Peplomycin at the same concentration resulted in a reduction of 5 % and 20 % of controls. The dose response curves of two probes from squamous cell carcinomas of the lung were almost identic. Insofar our experiments coroborate the findings with the HeLa cells and Ehrlich cells that Peplomycin is more cytotoxic than Bleomycin. However, individual drug sensitivity of human tumors must be considered.

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VBR 27

TUMOR-ASSOCIATED OSTEOPENIA (RAT): INFLUENCE OF OSTEOLYTIC TUMOR FACTORS AND TUMOR-HOST-REACTION

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The newly developed animal model of "Inflammation Mediated Osteopenia"(IMO)(Minne et al.,1984,Endocrinology,115:50) is based on the observation , that nonspecific inflammation due to s.c. talcum injections leads to a systemic loss of trabecular and compact bone. This rises the question to which extent inflammatory tumor host reactions may account for bone destruction in malignancy. We determined bone mass in rats after s.c. transplantation of the hypercalcemic variant of the Walker carcinosarcoma 256 (HWCS 256)(Minne et al. 1975,Acta Endocr 78:613)and the non-hypercalcemic Yoshida sarcoma (YS). Similarly bone loss was compared after inflammation either due to s.c. talcum injections(IMO) or tumor necrosis (frozen tumor implantation).Furthermore we investigated whether IMO adds to the bone loss in rats with HWCS 256.We applied computer-assisted x-ray analyses,bone-ash and -calcium measurements and histomorphometry to determine bone mass in groups of 10-15 rats. Results of computer-assisted x-ray analyses (pixels/bone area)(Bauss et al.1985, Calcif Tissue Int,37:539) are:Experiment 1:Control rats:6900+1150; rats with IMO:5850+1250;rats with HWCS 256:5100+2150;rats with IMO plus HWCS 256:4250+1750.Experiment 2:Controls:6750+650;rats with IMO:6250+1050;rats with YS:6150+1100;rats with necrotized YS:5450+1450.Conclusions:Malignant tumor growth leads to bone mass reduction, either induced by humoral osteolytic tumor products(HWCS 256),by inflammatory host reactions, or even by both mechanisms.

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VBR 28

TUMOR INHIBITING EFFECTS OF OSTEOTROPIC CYTOSTATICA LINKED BISPHOSPHONATES IN A RAT OSTEOSARCOMA

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1-Amino-3-hydroxypropane-1,1-bisphosphonic acid (APD), N-methylaminomethane-bisphosphonic acid (MAD), and the two bisphosphonates linked to cytostatic compounds diglycidyl-[3-(3,3-bisphosphono-3-hydroxypropylamino)-2-hydroxypropyl]-urazol (DDU) and 4-[4[bis-(2-chloroethyl)amino]-phenyl]-1-hydroxy-butane-1,1-bisphosphonate (BAD) were tested in equitoxic i.v. doses in a rat osteosarcoma model. 99m Tc-labelled APD, MAD and DDU showed high and rapid uptakes in bones, osteogenic primary tumor and in lung metastases. 77 Br-labelled BAD showed a delayed, but clearly visible uptake in bone, primary tumor, lung metastasis and liver. Treatment of osteosarcoma bearing rats with APD (10 x 1 7.5, resp. 2 x 23,5 mg/kg) - MAD (10 x 6.38, resp. 2 x 12.5 mg/kg) and DDU (10 x 49.4, resp. 2 x 98.8 mg/kg) did not result in prolongation of median survival time or reduction of tumor volumes. BAD treated animals (10 x 36.5 mg/kg) showed an increased median survival life time (228 T/C%) and a deceleration in tumor volume doubling time ($p < 0.001$) with 33.7 days (28.2 - 42.0) versus untreated control animals with 11.5 days (11.0 - 12.1). Acute intravenous toxicity of BAD is 146 mg/kg (DL50) and is probably caused by hypocalcemia after bolus injection. Subacute toxic effects in BAD treated animals had not been observed. Our investigations demonstrated the possibility to link two compounds with different principles of action, maintaining thereby - at least partially - the individual functions.

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VBR 29

THERAPY AND PROPHYLAXIS OF EXPERIMENTAL TUMOR INDUCED BONE LESIONS BY BISPHOSPHONIC ACID (APD) IN THE RAT

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Walker carcinosarcoma ascitic cells were inoculated in the arteria carotis (10^7 cells) or in the bone marrow cavity of the tibia ($2x10^6$ cells) of rats. APD was given intravenously as single doses (9.5 mg/kg: 24 h before or 24 h or 6 days after intravenous tumor inocculation) or in repeated doses 5x9.5 mg/kg on day 1 to 5 after intraarterial tumor inocculation. In a third mode five iv doses per week (5x9.5 mg/kg) were given 8, 4, 2 or 1 weeks before intraosseous tumor inocculation. Bone destructions were controlled by x-ray and histologically. Experiments showed a complete prevention of bone metastasis in the intraarterial model by APD. Single APD-doses in the intraosseous model gave best results by 24 hours pretreatment (80% reduction), followed by 24 hours posttreatment (40% reduction), whereas 6 days posttreatment showed no significant reduction. Long-term pretreatment (4, 2 or 1 weeks) resulted in complete prevention of bone destructions and pretreatment 8 weaks before intraosseous tumor inocculation still reduced bone destruction significantly. In conclusion, our animal models are useful for therapy experiments in tumor induced bone destructions. APD showed strong therapeutic and prophylactic effects in this models and is effective in the early osteoclastic mediated phase of tumor induced bone destruction, and less effective in the later phases.

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