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THE SUBRENAL CAPSULE ASSAY (SRCA) IN NUDE MICE, IMMUNOCOMPETENT AND PRE-IRRADIATED NORMAL MICE. H. Weigelt, H.H. Fiebig, C. Schuchhardt, U. Dentler and G.W. Löhr

The implantation of human tumors beneath the renal capsule of mice has been proposed by Bogden et al. to test new drugs and to determine the responsiveness of patients' tumors. The SRCA was first developed for nude mice with evaluation after 11 days and recently, for normal mice with termination after 6 days. The use of normal mice raises the question as to what extent the effect of an immunologic host response might have on the growth of the tumor explants.

We report on our experiences in transplanting 6 tumors directly from the patients and 13 from tumor lines in nude mice. Upon histological examination the tumors growing in nude mice showed various amounts of tumor cells, fibrous tissue and necrosis. From the 6 tumors derived directly from the patients only a melanoma and a sarcoma consisted of a viable homogenous tumor without necrosis. The other tumors were not suitable for the SRCA.

Implantation into normal mice showed that immune response began after 3-4 days, after 6 days 80 - 100% of the tumors was infiltrated by lymphocytes. According to our results, the SRCA is not suitable in normal mice. The immune response can be delayed for 6-8 days by total body irradiation with 9 Gy and bone-marrow restoration, both given 2 weeks prior to transplantation. The SRCA is a suitable short test procedure only in nude mice to test new drugs in established selected tumors. It has no value when tumors removed directly from the patient are studied.

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TRANSPLANTED DUCTAL PANCREATIC CARCINOMAS IN NUDE MICE-BIOLOGY, IMMUNOSCINTIGRAPHY, THERAPY (MONOCLONAL AB., CYTOSTATICS, IMMUNOMODULATION). R. Klapdor, U. Klapdor, M. Bahlo, H. Greten, M. Dietel, R. Montz, B. Kremer, J. Dimigen, J. Köhl, S. Lander, C. Ufer

In order to have an experimental model to study various diagnostic and treatment modalities before application to humans we started to establish human exocrine p.ca. to nude mice. Our present available data suggest that these transplanted tumors represent a valid experimental model. Take rate: 80-90%; histology, grading, immunohistochemistry and profile of the serum markers correlate well with the situation in the humans. As in the humans the results of immunoscintigraphy depend e.g. on tumor size, affinity of the tumor to the antibodies injected (anti-CA 19-9, anti-CA 125, anti-CEA) and on background activity. The treatment studies were done with various cytostatics, labelled monoclonal antibodies (J^{131} -anti-CA 19-9 or -CEA i.v. or i.t.) or immunomodulation as interferon, interleukin II or TNF. The results seem to confirm our clinical impression that the main points responsible for the insufficient clinical results have to be seen in a heterogeneous behaviour of the individual p.ca. against the various treatment modalities and in dose-dependent effects of the agents tested. The individual tumors showed a rather different behaviour without correlation to the biological parameters tested.

This animal model therefore might be of clinical value for an individual handling and treatment of human pancreatic carcinomas.

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INTERACTION OF CANCEROSTATIC DRUGS IN VITRO R. Hackenberg, G. Roche (a.G.), F. Hölzel, K.-D. Schulz

In polychemotherapy the combination of drugs is generally based on clinical experience. From the experimental point of view there is only limited knowledge on the rationale for commonly used combinations. The present study was designed to investigate the interaction of two antineoplastic drugs which are often applied in combination. Adriamycin (ADR) and cyclophosphamide (CYC) were tested on the permanent human mammary carcinoma cell line EFM 149.

The inhibition of proliferation was measured by cell counts after incubation periods of 1 to 9 days. A 50% inhibition was defined by the reduced increase of cell number in treated cultures versus control cultures. The ID₅₀ after an incubation of 3 days was determined at 0.05 µg/ml ADR or 0.42 µg/ml CYC (in its activated form). When the time of incubation was extended up to 9 days, the ID₅₀ of ADR decreased in a time-dependent manner to 0.0085 µg/ml where as the ID₅₀ of CYC was constant.

In a second series of experiments ADR and CYC were applied in varying combinations. An inhibition by 75% was achieved by the following combinations during the 3-day treatment schedule:

ADR	0	0,016	0,058	0,13 (µg/ml)
+	+	+	+	+
CYC	1,8	1,4	0,36	0 (µg/ml)

Over the concentration range tested both drugs acted in an additive manner.

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EXPERIMENTAL ACTIVITY OF THE ANTIESTROGEN ZINDOXIFENE J. Stekar, P. Hilgard, J. Pohl, T. Reissmann and R. Voegeli

Following parenteral or oral administration, 5-acetoxy-2-(4-acetoxyphenyl)-1-ethyl-3-methyl-indole (zindoxifene, D 16726, NSC 341952) exerts antitumour activity in several estrogen-dependent experimental tumours (E. von Angerer, J. Prekajac and M. Berger, Eur. J. Cancer Clin. Oncol. 21, 531, 1985). Throughout the present investigations a new oral formulation of zindoxifene was used. The bioavailability of this new form was considerably improved over previous preparations. Dose-response relationship studies were carried out using the DMBA-induced, autochthonous mammary carcinoma in rats and a standard 28 days treatment. The optimal dose of zindoxifene was found to be 10 mg/kg body weight. Under identical experimental conditions equimolar doses of tamoxifen citrate were less active. When suboptimal doses of both tamoxifen and zindoxifene were administered simultaneously, neither additive nor synergistic effects were observed. The antiestrogenic activity of zindoxifene was confirmed by the inhibition of the uterotrophic action of 17-β-estradiol in infantile rats. In contrast, high doses stimulated uterine growth indicating that the compound has some remaining estrogen activity. Acute and subacute toxicity studies in rats revealed that pharmacologically active zindoxifene doses were well tolerated even when administered daily over a period of 13 weeks. The pharmacological and toxicological profile of zindoxifene suggests that clinical studies are warranted.

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