Int 07

PHASE II STUDY OF A COMBINATION THERAPY WITH HUIFN-ALPHA, VBL, TAMOXIFEN IN THE ADVANCED RENAL CELL CARCINOMA (RCC)

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Introduction: In the chemotherapy of the advanced RCC VBL and HuIFN-alpha are the most active agents for which a response rate (PR,CR) of about 20% is claimed. (R.A. Kempf, Proc Ann Meet Soc Clin Oncol,3:59,1984) Several studies with tamoxifen report a remission rate of about 5% to 10% (V.J. Lanteri, Urol.,9:623-625, 1982). An additional effect of VBL and HuIFN-alpha in vitro was described (M.S. Aapro, Exp Chemotherapy, AACR Abstracts, 725,1982). Treatment plan: VBL 6mg/m²i.v. on day 1,8 and 15, HuIFN-alpha 5 Mio IU/m²s.c. three times a week for 4 weeks, tamoxifen 15mg/m²p.o.daily for 28 days. On day 29 the cycle was restartet. Re-evaluation after a minimum of 2 cycles. In cases of no change the therapy was continued until the tumor progressed. Criterias for patients entry: histologically confirmed RCC, documented progressive disease. Exclusion criteria: brain metastases, previous chemotherapy, prior irradiation. From 9/84 to 9/85 24 pts entered the study. 20 pts are eligible, 16 males, 4 females, median age of 54 years, median Karnofsky PS 85%. In 4/20 pts the primary tumor was unresected. Results: No CR, no PR were achieved, stable disease occurred in 12 pts (60%), 8/12 with metastases only of the lung. 8/20 showed contineously progressive desease. 5/20 died (3 with progressive disease, 2 with no change after two cycles). The median survival of the group with stable disease was 25+ weeks. The median survival of the group with progressive disease was 17+ weeks. Toxicity was acceptable: 6 pts showed leukopenia 2000. 1 pt achieved a severe peripheral neurotoxicity, grade III WHO and VBL had to be stopped in the second cycle. Despite some antitumor activity has been observed it can be concluded that the combination of VBL/HuIFN-alpha/tamoxifen in these doses and this regime is ineffective in pts with metastatic RCC and documented progression before treatment.

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Int 08

CYTOTOXICITY OF RECOMBINANT LEUKOCYTE A INTERFERON ON HUMAN CLONOGENIC TUMOR CELLS AND HUMAN BONE MARROW PROGENITOR CELLS IN VITRO

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Cells from 20 human tumor samples that were used immediately after resection and two tumors implanted in nude mice (malignant melanoma, sarcoma, colon carcinoma,ovarian carcinoma, squamous-cell carcinoma of the lung) were cultured in a methylcellulose monolayer assay (1). Single cell suspensions were obtained by mechanical disaggreation. Recombinant leukocyte A interferon (IFL-r A, kindly supplied by Hoffmann-La Roche, Basel) at concentrations of $10\text{-}10^4$ U/ml was added. Incubation was performed in 7,5 % CO_2 at 37°. After 8-10 days of culture the colonies were scored under an inverted microscope.
At a final IFL-r A concentration of 10^4 U/ml in one group colony formation was reduced between 70 % and 30 % compared to controls and in another group between 20 % and 5% respectively. In five tumors at 10^4 U/ml colony formation was inhibited completely. In contrast to the heterogeneous reaction of the individual tumors the incubation of 7 different normal bone marrow progenitor cells (CFU-C) revealed homogeneous dose-response curves independent from donor. At a IFL-r A concentration of 10^4 U/ml colony formation was reduced to 10 % of the control.
We conclude that the direct cytotoxicity of IFL-r A is dependent from individual properties of the tumors.

Literatur (1): Neumann et al.:
Tumor colony formation from human spontaneous tumors in a methylcellulose monolayer system.
Res.Exp.Med. 184, 137 (1984).

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ML 02

MAIN LECTURE

LEUKEMOGENESIS BY VIRAL ONCOGENES

Studies conducted over the last 5 years have shown that the activation of cellular oncogenes plays a key role in the origin of neoplasias. Although in most human cancers retroviruses are not implicated, they are excellent models to study oncogene-mediated cell transformation in mammalian cells. Two models of retrovirus-induced carcinogenesis can be distinguished in animal systems: 1) activation of cellular oncogenes by viral integration and 2) transmission of oncogenes by acute leukemia / sarcoma viruses. We have investigated the second mode by asking how avian acute leukemia viruses transform hematopoietic cells and how certain combinations of viral oncogenes can lead to more highly malignant cell phenotypes.

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Onc 01

ROLE OF ONCOGENES IN HUMAN TUMOR CELLS

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One of the major breakthroughs in the analysis of tumor formation was achieved by the detection of oncogenes. They were first discovered in retroviruses which are capable of inducing tumors in animals and transforming cells in culture. Viral oncogenes are derived from normal cellular progenitor genes, so-called proto-oncogenes, which are present in every normal cell. Derivatives of these proto-oncogenes which highly resemble the viral oncogenes were detected in many human tumors or tumor cell lines. Understanding of their mode of action comes primarily from the analysis of viral oncogenes. About two dozens of them are known today. Some of them (e.g. src) are related to either growth-hormones or growth hormone receptors which exhibit tyrosine-specific protein kinase activity. Phosphorylation signals are transmitted from the cell membrane to the nucleus through a series of unknown event. They result in loss of growth control and proliferation. The oncogenic hormone receptors differ from their normal counterparts by loss of hormone control and are therefore constitutively turned on. A second set of oncogenes (e.g. myc) code for nuclear proteins which seem to influence gene regulation by interaction with the cellular DNA. Altered gene regulation results in malignant transformation. A third group of oncogenic proteins (e.g. mil) seem to act by signal transmission in the cytoplasm through serine/threonine protein kinase activity. All three types of proteins are being characterized biochemically to understand their molecular mechanisms. Several oncogene proteins were molecularly cloned and expressed in bacteria. Polyvalent as well as monoclonal antibodies are being produced. Human tumor cells or tumor tissue are presently tested by various antibodies to determine to which extent oncogene proteins are useful as tumor markers or tumor progression markers. The myc protein is a candidate marker for the variant form of small cell lung cancer.

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