CPh 08**SIGNIFICANCE OF PROLACTIN (PRL) RECEPTOR DETERMINATION IN BREAST CANCER**

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The mammary gland is a target organ for PRL. The glandular cells transform the signal of the PRL molecule through PRL receptors which consist of integral membrane protein complexes. Cancers arising from mammary tissue may retain the ability to express PRL receptors. In plasma membranes derived from human breast cancers the range of PRL receptor concentrations was 0-45 fmol/mg protein. In plasma membranes derived from 40 dimethyl-benzanthrazene (DMBA) induced rat mammary cancers the range of PRL receptor concentrations was 0-200 fmol/mg protein. In several tumors of either origin the PRL receptor concentrations were very low and the definition of a "positive" PRL receptor has not yet been elaborated. Establishing a "cut off" point of 20 fmol/mg protein the incidence of "positive" PRL receptors was about 30% in human and 80-90% in DMBA induced rat mammary cancers. In livers of immature female rats PRL receptor synthesis is induced by estrogens. In human breast cancer tissues PRL receptor concentrations did not show any correlation to the presence of estrogen and/or progesterone receptors. The significance of PRL receptors for the biological characterization of mammary cancer is under investigation. From laboratory experiments and from clinical experience the following effects of PRL should be mediated via the PRL receptor: a) the growth promoting effect, b) the growth inhibiting effect, c) the negative prognostic influence of and d) the therapeutic resistance in hyperprolactinemia.

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CPh 09**5-FLUOROURACIL(FU) METABOLISM IN VIVO: AN APPROACH FOR A RATIONAL TREATMENT WITH FLUOROPYRIMIDINES.**

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5-Fluorouracil(FU) has been introduced into cancer chemotherapy almost 30 years ago. In recent years improved analytical methods have allowed a better understanding of the various metabolic pathways and of possible mechanisms of action. Although inhibition of thymidylate synthetase and incorporation into RNA are the most likely mechanisms of action, there may be other mechanisms as well. For the action of antimetabolites adequate activity of enzymes and adequate concentration of substrates and cosubstrates are crucial. Since these parameters vary widely depending on the biological material studied the vast majority of experimental results especially those from in vitro studies may not be relevant for the clinical situation. On the other hand in vivo studies of FU metabolism had to be restricted to animals because of the use of radiolabeled drug. FU pharmacokinetics in cancer patients were studied with various schedules and dosages. The plasma half-life ranged from 5 to 26 min. While this was not schedule-dependent, it correlated positively with the dose given. Despite a wide range, there was no correlation between the area under the curve(AUC) and the objective and subjective toxicity recorded. Hence, the amount of toxicity may be determined by the way and speed of metabolic conversion rather than the actual drug levels. ¹⁹F NMR spectroscopy was used to determine and quantitate FU metabolites in urine and plasma(for details see Port,R.E. et al. these proc.). This allows a detailed analysis of the FU catabolic pathway in vivo. It may help to identify other mechanisms of action and toxicity. Furthermore, introduction of biochemically modulating agents may be possible on a rational basis.

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CPh 10**THE IMPORTANCE OF POLYGLUTAMATE FORMATION FOR THE EFFICACY OF METHOTREXATE THERAPY**

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To get a better insight into the mechanism of methotrexate (MTX) action, we measured the concentration of unchanged MTX and of methotrexate polyglutamates (MTX-Gn) in sarcoma tissue and erythrocytes of patients under/after high-dose methotrexate therapy (HDMTX). Tumor specimens were removed 6-14 days after HDMTX in the context of surgery of the primary tumor or of metastases. In the tumor specimens MTX ranged from 7×10^{-8} M to 3×10^{-7} M thus exceeding the corresponding serum levels by a factor of 7-38. MTX-Gn could be detected in each case. Their portion of total tumor MTX, however, varied considerably between 3% and 68%. We tried to correlate the clinical results with the extent of MTX-Gn formation: Patients with MTX-Gn below 25% of total tumor MTX showed a rapid progression or early relapse of their sarcoma. Kinetics of erythrocyte MTX was triphasic. After the HDMTX infusion erythrocyte MTX drops down rapidly and starts to reincrease when the bone marrow releases freshly prepared erythrocytes containing MTX and MTX-Gn. Maximum values on days 10 - 14 are followed by the final efflux of MTX and MTX-Gn. Unchanged MTX revealed a rapid efflux with half-lives of 3 - 9,5 days. MTX-Gn, however, declined very slowly. With half-lives between 15 and 60 days they amount to nearly 100% of total erythrocyte MTX after 6 or more weeks after the last HDMTX infusion. These results confirm high MTX and MTX-Gn concentrations in sarcoma tissue and long-lasting storage of MTX-Gn in erythrocytes after HDMTX. As MTX-Gn remain strong folate antagonists, we believe that they play a major role in the principles and effectiveness of HDMTX therapy.

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CPh 11**CLINICAL PHARMACOLOGY AND METABOLISM OF MITOXANTRONE**

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Mitoxantrone (M) has shown activity in breast cancer, lymphoma and leukemia. Reported pharmacokinetic and metabolic data are controversial. We have studied the metabolism of M after incubation with liver microsomes, in the isolated perfused rat liver, in rat hepatocyte culture and in man. Our HPLC-system consisted of acetonitrile-water 25:75 (v/v) containing 5mM 1-pentanesulfonic acid on RP C-18 columns at a detection wavelength of 658 nm. The sample clean up was performed on XAD columns. Incubation with rat and guinea pig liver microsomes suggested that M is not metabolized. In the isolated perfused rat liver M was rapidly metabolized and three metabolites were separated. Metabolite formation was also observed in rate hepatocytes in primary monolayer culture. Four metabolites were separated in human urine. The major metabolite cochromatographed with the synthesized dicarboxylic acid of M (M1) and one other with the monocarboxylic acid analog (M2). Within 48 hrs. 4.4% of the administered dose of 14 mg/m² was excreted in urine as M, 0.5% as M1 and 0.3% as M2 (n=16). Urine and serum concentrations were analysed simultaneously with the aid of TOPFIT program. The pharmacokinetic parameters are adequately described by a three compartment model with a terminal half-life of 214 hrs., and a volume of distribution (ss) of 3792 L (n=7). The differences in metabolism in in vitro and in vivo studies may be caused by enzyme inhibition, P-450 independent pathways or the necessity of the intact subcellular organization.

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