NCy 23

ANTITUMOUR PROPERTIES OF VARIOUS (ALKYL)-LYSOPHOSPHO-LIPID ANALOGUES IN RAJI LEUKAEMIC CELLS

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Aim of research: (Alkyl)-lysophospholipids (ALP) have very different biological properties. We synthesized a broad spectrum of derivatives to learn more about the structural requirements in the cytotoxic action of ALP. Additionally, we determined substrate properties of the compounds to O-alkyl cleavage enzymes (C. Unger et al., Cancer Res. **45**, 616, 1985), acyltransferase and phospholipase C.

Methods: Raji cells (human leukaemic B-cells) were incubated with increasing amounts (1-50 µg/ml) of ALP derivatives up to 72 hours. The cytotoxic activity was characterized by inhibiting the (3H)thymidine incorporation into DNA, and with the trypan blue dye exclusion test. Substrate properties of the compounds were determined with phospholipase C (*Bacillus cereus*), acyltransferases and O-alkyl cleavage enzymes from rat liver microsomes.

Results: Destruction of Raji cells was observed with varying amounts of the test agents with half lethal doses (LD50), ranging from 2 to 45 µg/ml after 72 hrs. In vitro incubations of the derivatives with phospholipase C, acyltransferase and O-alkyl cleavage enzyme revealed remarkable differences in the substrate properties of the compounds. Highly active molecules in the destruction of leukaemic cells are no or only poor substrates for the O-alkyl cleavage enzyme or the acyltransferase. On the other hand, phospholipase C acts on all derivatives, which are cytotoxic to the leukaemic cell, whereas loss of phospholipase C hydrolysis results in loss of cytotoxicity.

Conclusions: No or very restricted substrate properties of ALP to the O-alkyl cleavage enzyme and/or the acyltransferase may result in antineoplastic properties of the compounds. Additionally, phospholipase C hydrolysis may be a prerequisite for the cytotoxic action of ALP.

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NCy 24

TOPICAL APPLICATION OF ETHER LIPIDS IN THE TREATMENT OF SKIN METASTASES

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Aim of research: Wide-spread local recurrence of breast cancer, intractable by surgery of radiation therapy, might present a serious therapeutic problem predominantly in patients refractory to systematic therapy. Ether lipids with high membrane affinity, in addition to their own antineoplastic activity, have been shown to enhance the penetration of chemo-therapeutic agents into cells (C. Unger et al., Klin. Wochenschr. **63**, 565, 1985). The present phase I trial in patients with extensive skin involvement of breast cancer was designed to test the antineoplastic activity and side-effects to normal skin of topically applied ether lipids.

Methods: Patients with skin metastases derived from breast cancer were treated with ether lipids twice daily.

Results: In a group of 9 patients, 4 showed objective tumour response, 2 a minor response, a further 2 partial remissions and one a complete remission. Although a mild dryness of flaking of the skin was observed, no systemic side-effects were noted.

Conclusion: These preliminary clinical results provide evidence that ether lipids may be effective in the treatment of skin metastases.

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NCy 25

PHARMACOKINETICS OF ETOPOSIDE IN ADULT PATIENTS WITH CANCER

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Etoposide and teniposide are semisynthetic epipodophyllin derivatives and have shown oncolytic activity in a variety of adult and pediatric leukemias and solid tumors. The pharmacokinetic knowledge about these compounds is limited although recently sensitive and quite specific methods were devised using HPLC with ultraviolet, fluorescence or electrochemical detection. Precise guidelines for dose modification of these drugs in patients with abnormal organ function have not been determined. Here we report plasma levels and pharmacokinetic parameters in adult tumor patients with various malignancies. The patients, all being treated with polychemotherapy, received etoposide on various days by iv-infusion. The doses ranged from 80-120 mg/m². Following extraction with chloroform, samples were separated by reversed phase HPLC or thin layer chromatography and etoposide was measured using a mass-spectrometer as a highly specific detector. For quantitation teniposide was used as an internal standard. In 16 patients we determined 28 one day plasma profiles of etoposide. Pharmacokinetic parameters were characterized using the appropriate multiexponential equations. We compiled the following data (mean ± SD):

Peak plasma level: 24.2 (±14.4) µg/ml; AUC: 4667 (±2144) µg/ml/min; $t_{1/2\alpha}$: 0.31 (±0.11) h; $t_{1/2\beta}$: 4.44 (±1.6) h; MTT: 6.1 (±2.1) h; V_d : 7.5 (±3.7) l/m²; Cl : 23.7 (±7.7) ml/min/m².

The $t_{1/2\beta}$ -half life times of etoposide measured with our method are the shortest ones reported so far. Only few investigators found similar values using an electrochemical detector. Much higher values for $t_{1/2\beta}$ were reported when the ³H-labeled compound was employed, apparently due to less specificity. Pharmacokinetic parameters were correlated to clinical data such as age, nutrition status, pretreatment, SGPT, Cl_{crea} , AP, serum albumin, γ -GT, and serum lipids. Significant influence could be shown for the following parameters: pretreatment with cis-platinum elevated AUC and decreased V_d and Cl , higher age correlated with longer $t_{1/2\beta}$ and elevated V_d^{ss} , bad nutrition status resulted in higher V_d^{ss} and Cl , and elevations of alkaline phosphatase and SGPT showed lower Cl .

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NCy 26

PHARMACOKINETICS OF THEPRUBICIN

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4'-O-Tetrahydropyranyl-adriamycin or theprubicin (THP) is a new anthracycline derivative which was equi-effective, but less cardiotoxic in preclinical testing compared to adriamycin. We are currently studying the clinical pharmacology of THP in patients with advanced malignant diseases. So far, we have treated 8 patients with colon cancer (n=1), acute myeloid leukemia (n=2), breast cancer (n=2), small cell carcinoma of the lung (n=1), and testicular cancer (n=2). The median age of these patients was 39 (range, 19-63) years. Two courses at each of the following dose levels have been evaluated: 30, 40, 50, and 60 mg/m². THP is given as an i.v. bolus injection every 3 weeks. Blood and urine samples were collected at specified times. THP was measured by a high-performance liquid chromatographic method that also allowed the analysis of the following metabolites: THP-adriamycinol (THP_{ol}), adriamycin (ADM), and adriamycinol (ADM_{ol}). Daunomycin was used as internal standard. The plasma concentration curve of THP showed a bi-exponential decay with an initial half-life ($t_{1/2}$) of 13±2 min (± standard deviation) and a terminal $t_{1/2}$ of 14±3 hours. A linear correlation between the dose and the peak plasma concentration and between the dose and the area under the curve was found. The volume of distribution was 2687±325 l/m² and the total clearance rate 139±29 mg/m²hr. The rate constant for the metabolism to ADM was calculated to 0.45±0.1 hr⁻¹. ADM had a terminal $t_{1/2}$ of 30±4 hr and the largest area under the curve of all 4 compounds. The $t_{1/2}$ of THP_{ol} was 21±3 hr and that of ADM_{ol} about 60 hr. The urinary excretion of THP amounted to 4±2 % (sum of all 4 compounds 18±7 %). In summary, the pharmacokinetics of THP could be described by an open two compartment model. THP was rapidly metabolised to ADM, but high peak plasma levels of ADM were avoided. We are currently entering patients at a dose level of 70 mg/m² into the study.

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