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COMPARISON OF P-GLYCOPROTEIN EXPRESSION AND DAUNORUBICIN CELLULAR ACCUMULATION IN ADULT AND CHILDHOOD ACUTE LEUKEMIAS

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Multidrug resistance of tumor cells is known to be responsive for treatment failure in cancer chemotherapy and P-glycoprotein (PgP) overexpression is suspected to correlate with the development of resistance phenotype.
Thirty-six blood and bone marrow samples from 21 adults (13 AML, 8 ALL) and 13 children (3 AML, 10 ALL) were analyzed using flow cytometry analysis with simultaneous determination of Pgp by MRK16 monoclonal antibody (kindly provided by Dr. T. Tsuruo, Tokyo, Japan) and accumulation of daunorubicin (DNR).
In the 23 samples from adult patients, the mean labeling rate by MRK16 was low (3.5%), 1.5% in the 16 patients with complete response, 8.1% in the 7 non responding patients. The rate of DNR accumulating cells was statistically higher in the responding pts than in non-responding patients (49.9 and 23.2% respectively, p=0.02). In the 13 samples from children patients, the mean labeling rate by MRK16 was 1.5% and the mean rate of DNR accumulating cells, 18.2%. In the 10 children patients with ALL and in complete remission, the rate of DNR accumulating cells observed (mean 14.5%) was significantly lower ($p<0.05$) than in adult ALL with complete remission (7 cases, mean 39.2%). From these results, if the rate of DNR accumulating cells seemed to be a predictive factor of clinical response in adult leukemia, in childhood leukemia, the threshold value may significantly differ and should be precised before attempting to extrapolate the results from adult to chilhood leukemias.
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COMPARATIVE EVALUATION OF S9788, VERAPAMIL AND CYCLOSPORINE A ON MULTIDRUG RESISTANT CELLS FROM PATIENTS WITH HEMATOLOGICAL MALIGNANCIES.

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S9788 is a new triazinoaminopiperidine compound (Servier, France) designed to circumvent multidrug resistance (MDR). When used at pharmacologically achievable concentrations in MDR cell lines, S9788 was found more potent than verapamil (VPL) and cyclosporine A (CSA). In the present study, we evaluated these three compounds at equimolar concentration (5 µmol/l) on bone marrow samples from 35 patients bearing hematological malignancies (leukemias, lymphomas or myelodysplastic syndroms) and compared their respective ability to reverse MDR phenotype using flow cytometry analysis with simultaneous determination of P-glycoprotein (Pgp) by MRK16 monoclonal antibody (kindly provided by Dr. T. Tsuruo, Tokyo, Japan) and accumulation of daunorubicin (DNR) in cells concomitantly exposed to the reversing agent. In Pgp-negative samples (18 cases), no significant effect of the reversing agents on DNR accumulation was noted. In the 17 Pgp-positive samples, significant increase in DNR accumulation, by at least one reversing agent was evidenced in 10 cases (60%). In all cases, S9788 was evaluated and was compared with both VPL and CSA (8 cases), VPL only (16 cases) or CSA only (9 cases). In 7 cases (70%), S9788 MDR-reversing activity was higher than the others, against 2 cases for VPL (20%) and 1 case for CSA (10%). These results further confirmed the potential usefulness of S9788 in circumventing MDR and its higher activity in clinical resistance when used at clinically relevant concentration. This study was performed within a cooperative work between the French Oncological Clinical Pharmacology Group and Servier International Research Institute and supported by the French "Ligue Nationale contre le Cancer".

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SENSITIVITY TO CYTOTOXIC DRUGS IN BIOPSY MATERIAL FROM LUNG CARCINOMAS

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Chemotherapy is the main treatment modality in small cell carcinoma of the lung (SCLC) and is of increasing importance also in non small cell carcinomas of the lung (NSCLC). Drug resistance is, however, very common in NSCLC and a major obstacle against cure in SCLC. A fluorometric microculture cytotoxicity assay for investigation of drug-resistance of biopsy derived tumourcells has earlier been used in certain leucemias and lymphomas and in these tumours the results of the assay have correlated well with the clinical outcome. Viable cells cleave fluorescein diacetate to fluorescent fluorescein and the effect of drug treatment on survival was measured after exposure for 3 days compared with the survival of unexposed cells. The assay has here been applied to biopsies from 12 lungcarcinomas. The sensitivity profile differs considerably between individual tumours, SCLC, however, beeing as a rule more sensitive compared with NSCLC. Cisplatinum was in these few tumours maybe the most effective drug, however, also etoposide and doxorubicine and other antracyclines demonstrated efficiency.

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POSITIVE CORRELATION BETWEEN TUMOUR DRUG DISPOSITION AND THE ACTIVITY OF DOXORUBICIN MICROSPHERES: IMPLICATIONS FOR THE DRUGS IN VIVO MECHANISM OF ACTION

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Protein microspheres can actively alter both drug disposition and the therapeutic properties of incorporated doxorubicin (DOX) once they have reached the tumour. This is due to the fact that a proportion of the drug becomes covalently coupled to the protein matrix of the microspheres during their formation and acts as a sustained release depot but reduces drug anaerobic quinone bioreduction (AQR). In this study DOX has been incorporated into 5 different formulations of microspheres where % complexation was: 0, 49, 69, 76 and 88 resp. Each system contained the same total drug content (2.2-3.2 % w/w) and achieved the same tumour total drug level at time zero after intra-tumoural injection to the rat Sp 107 mammary carcinoma (15-17 µg/g). There was no correlation between fold stimulation in AQR over the levels produced by free DOX (83, 81, 26, 14, 0 resp.) and tumour growth delay in days (4.5, 7.4, 6.8, 12, 12 resp.). A strong correlation (r^2 =0.948, $P < 0.01$ two tailed t statistic) was observed between slow release of native drug and antitumour efficacy. These data support the view that free radicals are not involved in the mechanism of action of DOX and suggest that the optimum way to deliver DOX to a tumour for maximum effect is through sustained release of lower concentrations (approx. 2 µM) from a large extracellular pool.

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CHEMOFILTRATION (CF) FOR LOCALLY ADVANCED CANCER

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Regionally advanced cancer is a common, often unresolved problem. Effective local control is limited by the toxicity of systemic chemotherapy. CF enables the administration of high dose cytotoxic drugs into one body area while limiting systemic toxicity. The drug is infused into the artery supplying the involved area. The venous effluent of the same organ is pumped out into a hemofiltration unit at a rate of 500ml/min. The drug is then filtered away and the blood returned to the systemic circulation. 41 pts. underwent 45 CF. 24 pts. underwent CF of the pelvis for advanced renal cancer (10), malignant melanoma (6), and cancers of the ovary (2), uterine cervix (3), vulva (1) and anus (1). 17 pts underwent CF of the liver for metastatic colon (10), pancreas (1), breast (4), ovary (1) and unknown (1) cancer. 5FU 1g/m^2/10min and mitomycin-C 30mg/m^2/20min; cis-platinum 200mg/m^2 alone or combined with bleomycin 50mg/m^2 and mitomycin-C 20mg/m^2; or melphalan 1mg/kg were the combinations used. 2 pts died within 40 days following CF. The procedure was generally well tolerated. Complications (48%) included transient leukopenia (16), paralytic ileus (2), ototoxicity (1), hair loss (2), renal failure (1). Of 39 evaluable patients, 17 (44%) had PR, 15 (38%) SD and 7 (18%) PD. Time to progression was 5.4mts. 10/13 (77%) achieved symptomatic palliation. In 12/24 pts (50%), a reduction in CEA levels occurred.