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CONTROL OF LEFT VENTRICULAR EJECTION FRACTION (LVEF)IN LOW VS HIGH DOSE-EPIRUBICIN (E)THERAPY.
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supported by Recherche sur le Cancer et les Maladies du Sang.
Since 1985 we performed several studies including E at different dose levels.LVEF was monitored for most of the patients (pts)at entry to the respective protocol and controlled during therapy.49 pts are evaluable,with at least 2 determinations of LVEF.23 have been treated in low-moderate dose intensive (DI)programs for E : DI per week(W) < 4o mg/m2/W;26were treated in high DI programs (> 4o mg/m2/W).Base-line LVEF value for the pts was 59% (SD:+/-9,5).The difference of LVEF at cumulative doses of < 6oo mg/m2 and > 6oo mg/m2 were calculated for each patient with respect to his base-line level.At < 6oo mg/m2 no significant difference was detected compared to base-line;at > 6oo mg/m2 a significant drop of LVEF was recorded.A significant difference for changes of LVEF between low and high DI regimens of E does not appear with the data available until now.

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PHARMACOKINETICS OF HIGH DOSE METHOTREXATE (HDMTX) INFUSION IN ADULT OSTEOSARCOMA.
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We had individualized dosage of HDMTX with a predeterminated and constant plasma level for each patient. 22 adults (mean age 26.5 ± 13.8) with osteosarcoma received 222 infusions of HDMTX over 8 H to achieve a theorical maximum value (Cmax) of 10^{-3} M/1. The mean dosage delivered was 22571 ± 3272.5 mg (13118 ± 2074 mg/sqm). Average peak concentration was 1015.67 ± 364.62 µmol/1. This value was not significantly different of the desired Cmax. The mean concentration at 23h and 47h was 30.34 ± 29.88 µmol/1 and 2.12 ± 3.14 µmol/1 respectively. The mean total body clearance was 49.1 ± 11.72 ml/mn/sqm. Average volume of distribution was 0.32 ± 0.8 1/Kg and the mean AUC was 4780 ± 1631 µmol/h/1. Mean T1/2α was 2.66 ± 0.82h and terminal half life was 15.69 ± 8.63 h. The initial T1/2 was correlated ($P < 0.001$) with MTX concentration at 23h (r=.54) and 47h (r=.48). Pharmacokinetic parameters and MTX plasma concentration were not correlated with hematologic and digestive toxicity when renal toxicity was correlated with T1/2α, MTX concentration at 23h and 47h. With this method severe toxicity (grade 3 and 4) were avoided and we suggest a wider application of clinical pharmacologic finding in the practice of the administration of HDMTX.

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PHARMACOKINETICS OF ETOPOSIDE: CORRELATION OF PHARMACOKINETIC WITH CLINICAL CONDITIONS
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The pharmacokinetic parameters of etoposide were established in 35 patients receiving the drug parenterally within the framework of different polychemotherapy protocols. A total of 62 data for 24-h kinetics were analysed. After sample extraction and HPLC or TLC , etoposide was measured by means of [^{252}Cf]-plasma desorption mass spectrometry (PDMS). This highly specific detection system proved to be very practicable and reproducible. The present study comprised two parts that were absolutely comparable in terms of clinical and pharmacokinetic parameters. In part II of the study, sensitivity was improved by modifying the analytical technique. After the exclusion of patients who had previously been given cisplatin or who exhibited renal impairment and of one patient who showed extremely high levels of alkaline phosphatase, γ-GT and SGPT, the mean values calculated for the pharmacokinetic parameters evaluated were; t1/2β, 4.9 ± 1.2 h; MRT, 6.7 ± 1.4; AUC, 5.43 ± 1.74 mg min ml^{-1}; Vd_{ss}, 6,8 ± 2.71 /m^2; and Cl, 18.8 ± 5.3 ml min^{-1} m^{-2}. The pharmacokinetic parameters were correlated with 12 different demographic or biochemical conditions. Impaired renal function, previous application of cisplatin and the age of patients were found to influence etoposid disposition to a statistically signifcant extent. We suggest that the dose of etoposide should be reduced in elderly patients and/or in individuals with impaired renal fuction, especially in those exhibiting general risk factors such as reduced liver function with regard to the polychemotherapy.

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LIFE-THREATENING MYOCARDIAL IMPAIRMENT INDUCED BY 5-FLUOROURACIL (5-FU)
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5-FU cardiotoxicity occurs in appr. 5 % of patients, is noncumulative and generally mild. However, four pts (age 38-62, 3 male, 1 female) with life-threatening cardiotoxicity while on conventional (550 mg/m²/d x 5, n=3) or high-dose (2600 mg/m²/d, n=1) 5-FU/folic acid (FA) schedules could be observed. Symptoms were unstable angina pectoris (3), ST elevation (3), ST depression (1), hypotension (3), pulmonary congestion (1), and dyspnea (1). All pts recovered from clinical symptoms within 48 hrs, while echocardiography showed severe global (3) or local (1) myocardial dysfunction for up to 7 days. One pt underwent coronarography showing small vessel disease.
Conclusions: 1. Rare cases of life-threatening 5-FU cardiotoxicity can present as unstable angina, myocardial infarction, or cardiogenic shock - it can occur in 1-day high-dose and in 5-day conventional dose schedules. 2. Echocardiography may reveal severe ventricular dysfunction despite normal ECG. 3. The pathogenetic role of concomitant FA remains open.

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CPT 11 : PHASE II-PHARMACOKINETIC STUDY IN BREAST CANCER PATIENTS
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The camptothecin analogue CPT 11 (IRINOTECAN), was studied in phase II in breast cancer patients (pts). We administered 350 mg/m2 CPT 11 as a 30 or 60-minute iv infusion once every three weeks. Till now, 25 pts with one previous curative chemotherapy regimen were entered. In order to determine pharmacokinetic (PK)-pharmacodynamic (PD) relationships, PK of CPT 11 and its active metabolite SN 38 were performed in the 25 pts (65 courses). The approximation of the PK parameters was performed with 3 blood samples (5 min. before the end of the infusion, 1 and 6 hafter the beginning of the infusion) according to the minimum sampling strategy, based the phase I data. Very important intra and inter-individual variations of the PK parameters of CPT 11 and SN 38 were observed. A certain correlation has been noticed between CPT 11 PK parameters and the toxic side effects of the drug.

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RESULTS OF A PHARMACOKINETIC (PK) STUDY OF IFOSFAMIDE (IFX) IN CHILDREN. HIGH VALUE OF AGE.
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Controversies about effectiveness of IFX in children are not yet resolved. The results of the German Group in Ewing's sarcoma (ES) showed a better result that previous study with cyclophosphamide (CPX). In contrast, the SFOP study in ES found no improvement in 3 y. DFS in their protocol with IFX instead of CPX. Furthermore, the combination of VAIA is an effective therapy in childhood RMS. A high IFX dosage of 10 g/sqm per cycle achieved a better response rate (83%) than a lower dose 6 g/sqm (68%). Backgrounds of these contradictions could be age and PK of IFX in children.
MATERIAL & METHODS : 48 patients (p.) aged 1,5 to 25 y. with various solid tumors, received 121 courses of IPA (IFX, CDDP, THP ADR) with seric PK study. IFX was infused continuously in 5 days (d.) (debit 1,2 g/sqm/d). IFX was dosed by gaz chromatography with thermoionic detection. 1850 dosages were computerized for statistical analysis.
RESULTS : Seric IFX reaches the steady state after 10-12 hours (h.) infusion. Half life increase is 4 h (min 2h30, max 7). No difference of mean seric level was found 1 day to another. For the daily infusion of 1,2 g/sqm, the average seric level is $12,15.10^{-3}$ g/l (min 6.5/max 20, s.d. = 2,5). The average seric IFX clearance is 72 ml/min (min 50/max 120), s.d. = 19). *Seric clearance is significantly correlated ($p < 0,001$) with age*. Young patients show a higher clearance and a lower seric concentration for a fixed dosage than older p.
CONCLUSION : Significant correlation of IFX clearance with age could explain lower apparent effectiveness in young children at fixed dosage. Further studies are needed to find the best Cplateau concentration or best AUC effective in different pathologies.