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INTRAPERICARDIAL CISPLATIN IN PATIENTS WITH MALIGNANT PERICARDIAL EFFUSION.

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Local treatment with cisplatin administered directly into pericardial space in patients with malignant pericardial effusion of various neoplasmatic etiology (**mainly with primary lung tumors**) were studied. After insertion of polyurethane catheter (Cavafix), fluid was drained and cisplatin was administered in 13 cases (10 mg of cisplatin in 20 ml of normal saline was instilled over 5 minutes during 5 consecutive days; total cisplatin dose=50 mg). If fluid reaccumulation had occurred, the courses of cisplatin were repeated every 2 or 3 weeks. In 11 patients (in 2 after 20 mg and 30 mg of cisplatin, in 8 after one course, in 1 after four courses) complete therapeutic response (no more fluid reaccumulation) was obtained. No effect (fluid reaccmulation) was achieved in 2 cases of intrapericardial cisplatin-therapy. No local, hematology or renal complications of treatment were observed. We believe, that in patients with malignant pericardial effusion of various neoplasmatic etiology, the intrapericardial administration of cisplatin is effective and safe.

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TOXICITY OF HIGH DOSE IFOSFAMIDE + MESNA WITHOUT COLONY STIMULATING FACTOR (CSF).

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Standard doses of ifosfamide (IFX) for solid tumors are between 5 and 8 g/m2 and a dose response relation has been observed. We describe the toxicity of a regimen with a dose of 14 g/m2 of IFX with mesna without CSF. Eight patients (pts) (5F-3M), median age 39 (r 25-65) with advanced solid tumors: soft tissue sarcomas: 3 pts, osteogenic sarcoma: 4pts, squamous cell carcinoma of the cervix: 1 pts.; were treated with IFX 3,2 g/m2 d 1 and 1,8 g/m2 d 2-7 + mesna 20% of IFX dose every 4 hours. A total of 11 cycles were delivered at full dose and 2 cycles were stopped at 9 g/m2 due to neurologic toxicity (1 pts) and high blood pressure (1 pts). Results: Haematologic toxicity: leucopenia G4: 3 cycles, thrombopenia G3: 1 cycle. Nausea and vomiting G2: 3 cycles; macrohematuria: 2 cycles; CNS toxicity G2: 1 cycle, paresthesias: 1 cycle. There were 2 episodes of short febrile neutropenia. No toxic deaths occurred. Three pts had a PR, 2 pts stable disease and 3 pts progresed.
Conclusions: IFX at this dose has moderate and reversible toxicity. The response obtained justifies to continue with this protocol. For this group of pts no CSF was needed.

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PHARMACOKINETICS AND TOXICITY OF ETOPOSIDE IN COMBINATION WITH CARBOPLATIN IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC).

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To study the relationship between pharmacokinetics and myelotoxicity of a combination of etoposide and carboplatin, pharmacokinetic parameters of carboplatin and etoposide were measured day 1 in 21 patients with SCLC, receiving etoposide 100 mg/m^2 on days 1-3. To achieve a uniform exposure of carboplatin, dose was calculated from the formula suggested by Calvert et al.: dose = AUC • (GFR + 25); GFR was measured by ^{51}Cr-EDTA-clearance and target AUC was 5 mg • min/ml. Blood samples were drawn before and multiple times after the infusions.

Pharmacokinetic analysis revealed a variation of almost a factor 2 in carboplatin AUC (mean 4.9±0.9, range 3.4-6.3 mg • min/ml). However, the variation in etoposide AUC was higher (mean 5.5±1.6, range 2.9-9.0 mg • min/ml). Multiple regression analysis with a sigmoid expression of the relative decrease in leuko- and thrombocyte counts [ln(% decrease/% surviving fraction)] as the dependent parameter and clinical and pharmacokinetic parameters as independent parameters revealed that etoposide plasma clearance was the only independent parameter selected for both leukocytes (r=-0.73) and thrombocytes (r=-0.60), whereas carboplatin pharmacokinetic parameters were not selected at all in the analysis. We conclude that, in the present regimen, the variation in etoposide pharmacokinetics was the main factor responsible for the variation in myelotoxicity and that, although higher than expected, the variation in carboplatin exposure was too small to explain any variation in myelotoxicity.

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PHARMACOKINETICS OF DROLOXIFEN COMPARED TO TAMOXIFEN

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Aiming at a comparative pharmacokinetical analysis between Tamoxifen and the new antiestrogen Droloxifen, 28 patients with metastatic breast cancer have been treated since 1985 with 40 mg p.o./d of the antiestrogens in a double-blind randomised study. During the first three treatment months and following to the end of the treatment, blood samples have been taken at well-defined times in order to investigate routine laboratory parameters as well as serum concentrations of Tamoxifen and Droloxifen and their metabolites. Due to its completely different metabolism pathway, the pharmacokinetic data of Droloxifen in serum show quick absorption, almost no accumulation and rapid elimination. This enables the substance to react sooner with its target resulting in shorter times to treatment effects compared to Tamoxifen. Finally the therapeutic flexibility will be improved.

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IS CREATININE CLEARANCE A SUFFICIENT MEASUREMENT FOR GFR IN CARBOPLATIN DOSE CALCULATION?

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The use of Calvert's formula (dose=AUC·(GFR+25)) permits pretreatment determination of carboplatin exposure. Furthermore, retrospective studies estimating the administered AUC (AUC=dose/(GFR+25)) may provide important information about relations between carboplatin exposure, toxicity and response. Calvert et al. recommend measurement of GFR by ^{51}Cr-EDTA-clearance. Other investigators tend to use creatinine clearance, which is a less ressource consuming method. We wanted to investigate whether the use of creatinine clearance actually produces a valid estimate for carboplatin AUC.

Before 62 courses of carboplatin and cyclophosphamide in 24 ovarian cancer patients, we measured pretreatment ^{51}Cr-EDTA-clearance as well as 24-h endogeneous creatinine clearance. Mean ^{51}Cr-EDTA-clearance was 86.3 (range 49.3-120.9) ml/min and mean creatinine clearance was 103.2 (range 57-165.9) ml/min. A paired T-test comparing creatinine clearance and ^{51}Cr-EDTA-clearance showed T=6.4 ($p < 0.00001$). Comparing observed car-boplatin AUC with estimated carboplatin AUC using creatinine clearance showed a high bias (MPE% = -13.1 ± 2.4%), whereas the carboplatin AUC estimated from ^{51}Cr-EDTA-clearance showed no bias (MPE%= -0.2 ± 1.9%).

We conclude that the use of creatinine clearance results in a systematic overestimation of GFR with a consequent underestimation of the actually administered carboplatin AUC in the retrospective studies, and, in pretreatment dose calculation, there is a risk of carboplatin overdosing.

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TAMOXIFEN SUPPRESSES THE PLASMA LEVEL OF THE ATHEROGENIC FACTOR HOMOCYSTEINE

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Long-term treatment of breast cancer patients with tamoxifen may reduce cardiovascular mortality. This has been explained by the more favourable lipid profile attained following tamoxifen exposure. We examined the plasma level of the atherogenic amino acid homocysteine in 31 postmenopausal women with breast cancer during treatment with tamoxifen. The plasma homocysteine level was decreased by a mean value of 29.8 % after 9 - 12 months and by 24.5% after 13-18 months of treatment. The reduction was most pronounced in patients having the highest pretreatment levels. Decrease in plasma homocysteine during tamoxifen treatment may contribute to the reduction in cardiovascular mortality observed among patients on adjuvant therapy with this drug.