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MEDROXYPROGESTERONE- AND MEGESTROL ACETATE PLASMA LEVELS AFTER SIMULTANEOUS ORAL ADMINISTRATION IN CANCER PATIENTS.

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Medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are used in the treatment of advanced breast cancer with "standard" oral doses of 1000 mg/day (range 500 - 5000 mg/day) mg/day and 160 mg/day (range: 160 - 1600 mg/day) respectively. We have developed an accurate and sensitive HPLC method to simultaneously determine both drugs in the plasma of patients.

To avoid the well described interpatient variability in progestin pharmacokinetics, 10 advanced cancer patients were treated with 1000 mg/day of MPA and 160 mg/day of MA *simultaneously administered* for 28 days. The mean steady state plasma concentration was 37 ng/ml (range: 3 ng/ml - 81 ng/ml) for MPA and 308 ng/ml (range: 88 ng/ml - 424 ng/ml) for MA. Terminal half-lives were 29 hours and 54 hours respectively. Relative MPA : MA bioavailability during the 28-day treatment (expressed as the ratio of dose-corrected AUCs) was 1 : 83 (range 1:36 - 1:147). Large amounts of MPA-derived glucoronides and/or sulphates were also present in the plasma samples. The extremely large difference in the relative bioavailability of the two drugs is very likely to be due to extensive hepatic first-pass metabolism of MPA, with differences in GI-tract absorption playing a minor role.

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TREATMENT OF TAXOL-INDUCED PAROXYSTIC PAIN SYNDROME WITH ANTIHISTAMINES

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Taxol is a very interesting novel cytotoxic drug. Its dose-limiting toxicity is represented by myelosuppression and neurotoxicity. One of the most troubling side-effects is a paroxystic pain reaction involving muscles and bones mainly in the lower extremities with or without painful dysesthesia (referred to as myalgia or arthralgia or as expression of neurotoxicity). The occurrence of this reaction was reported in up to 96% of the patients treated with taxol and, in some cases, the intensity was so severe as to require treatment with narcotics. The physiopathological mechanism remains unclear and a specific treatment is not yet available. In our experience 6/9 patients (5 ovarian and 4 breast cancer) treated with taxol (135-175 mg/sm by 3-hour i.v. infusion every 3 weeks) developed moderate-to-severe pain. Overall, 4/6 patients experienced complete relief of symptoms with one or two tablets of an antihistamine (mebidroline 50 mg or terfenadine 60 mg at pain onset). 2/4 complete responders had had only partial remission of pain with high dose NSAID during previous taxol cycles. A partial reduction of pain was evident in one patient while no benefit was obtained in another. Treatment with oral antihistamines seems to be effective without significant side-effects in controlling taxol-induced myalgia-dysesthesia. Since the use of taxol will probably expand in the next few years, this preliminary observation should be investigated in depth.

Drug Resistance

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MDR1 GENE EXPRESSION IN ACUTE MYELOID LEUKEMIA

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The expression of the MDR1 gene was determined in the leukemic cells of patients with acute myeloid leukemia (AML) at diagnosis and correlated with clinical outcome. MDR1 RNA expression was negative in 37% and positive in 63% of the patients (N=79). The complete remission (CR) rate of induction chemotherapy was 54% for the positive patients and 76% for the negative patients (P=0.05). The duration of overall survival (OS) was 8 months for the positive patients and 19 months for the negative patients (P=0.03). P-glycoprotein expression was determined by means of monoclonal antibody C219 in 52 patients. In patients with 0-5% staining cells, the CR rate was higher (74% vs. 40%, P=0.01) and the duration of OS was longer (15 months vs. 6 months, P=0.1) than in patients with >5% staining cells. The data suggest that the MDR1 gene is a clinically relevant drug resistance gene in AML and that reversal of multidrug resistance should improve clinical outcome in this disease.

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EXTRACELLULAR ATP REVERSES DRUG EFFLUX MEDIATED BY THE P-GLYCOPROTEIN.

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The multidrug resistance (*mdr1*) gene product, P-glycoprotein, is responsible for the ATP-dependent extrusion of a variety of compounds, including chemotherapeutic drugs, from cells. We have recently shown (Abraham et al *Proc Natl Acad Sci 90, 312-316 [1993]*) that cells with the P-glycoprotein release ATP into the medium and have ATP-conducting channels in the plasma membrane. Here we present evidence that the release of ATP by cells with the P-glycoprotein is increased in the presence of excreted compounds and that the secretion of adriamycin is inhibited by the presence of extracellular ATP. These results support the view that the transmembrane electrochemical gradient of ATP provides the driving force for drug excretion through the P-glycoprotein.

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RESISTANCE FOR IRRADIATION OF CARBOPLATIN RESISTANT HUMAN OVARIAN CANCER CELLS.

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The combination of carboplatin (CBDCA) and ionizing radiation is increasingly used in the clinic, yet resistance of tumor cells to both treatments is a basic problem in oncology. Resistance patterns to CBDCA and to irradiation were investigated in a human ovarian cancer cell line (AOvC-O).

AOvC-O cells grew in a monolayer and were cultured at 37°C. Cultures were irradiated with cobalt-60 (dose range 1- 8 Gy). Cell sensitivity was assessed with a clonogenic assay. Resistance to CBDCA was induced in the AOvC-O cells by continuous exposure to increasing concentrations of the drug in the culture medium. The cells became resistant to 8 µM CBDCA and continued to grow at this concentration. The resistance proved to be stable after withdrawal of the CBDCA pressure from the culture medium.

Cells resistant to 8 µM CBDCA were less sensitive for ionizing radiation than the parental cells at all doses applied. The resistance factor at the 10 % survival level was 1.8. The cross-resistance was stable after withdrawal of the drug from the culture medium . Besides, these CBDCA resistant cells were found to be cross-resistant for cis-Diamminedichloroplatinum (CDDP).The differences in sensitivity could not be explained by alterations in cell kinetics. Other underlying mechanisms are still under study.

We conclude that chronic exposure to CBDCA resulted in a decrease in radiosensitivity as compared to the parental cell line. The differences in sensitivity for irradiation and CDDP between the parental and the CBDCA resistant cells might have possible clinical implications.

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CLINICAL RELEVANCE OF P-GLYCOPROTEIN IN LEUKEMIA-PATIENTS

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We have examined 122 samples of patients with acute nonlymphoblastic leukemia, 61 patients with acute lymphoblastic leukemia (ALL), 32 patients with chronic myelogenous leukemia (CML) by P-glycoprotein (P-170) expression. We used the monoclonal antibody (mAb) C219 that binds to an internal epitope and with the mAb MRK16 that binds to an external epitope of P-170. The specimen was considered P-170 positive when 15% or more cells were stained.

At primary diagnosis 28 patients (23%) of 122 with AML were P-170 positive but no ALL-patients. 89 of 102 AML-patients (87%) with a low P-170-expression in bone marrow (BM) showed a response to daunorubicin/vincristin/ara-C-treatment. 4 of 16 AML-patients (25%) with a high P-170-expression demonstrated no response to the above-mentioned treatment. The predictive value for a response under the condition of a low P-170-expression is 87% and for non-response 80%. In addition to that we showed for the first time P-170-induction after treatment in AML/ALL-patients after daunorubicin/vincristin-treatment. 21 CML-patients in chronic phase except 4 patients had a normal P-170 expression. Those 4 patients showed a short transition time to the accelerated phase or blast crisis respectively. 5 of 11 CML-patients in blast crisis were P-170 positive and no response to vincristin/prednisolone or to the VAD regime was observed. 3 of 6 CML-patients with normal P-170 expression had a response to the above mentioned therapy.