776C was calculated from the ratio (F) of FU IC50 without 776C divided by FU IC50 with 776C. 776C was not cytotoxic to any of the cell lines tested. On CAL51 cell line, expressing a high basal DPD activity, FU enhancement by 776C was a saturable phenomenon related to the 776C concentration; the inhibition of DPD increased between 10^{-12} to 10^{-6} M of 776C. For the following studies, 776C was tested at 10^{-6} M. FU IC50 varied from 15 to 7770 μM among cell lines (median 390 μM). Basal DPD activity ranged from not detectable (< 1 pmol/min/mg prot) to 320 pmol/min/mg prot among cell lines (median 53 pmol/min/mg prot). For the 12 cell lines tested, the mean F ranged from 0.7 (no enhancement of FU cytotoxicity by 776C) up to 5.2 and was significantly related to the basal DPD activity: the greater the DPD activity, the greater the FU enhancement factor (Spearman rank correlation, $P = 0.019$). Enhancement of FU cytotoxicity by 776C occurred only in the 6 cell lines expressing the greatest basal DPD activity (> 50 pmol/min/mg prot, F ranging between 1.7 and 5.2), whereas 776C did not modify FU cytotoxicity in the remaining cell lines expressing the lowest DPD activity (< 50 pmol/min/mg prot, F ranging between 0.7 and 1.4); F was significantly different between these 2 groups of cell lines ($P = 0.005$). These results justify clinical trials with DPD inhibitors like 776C.

131 POSTER

CLINICAL RELEVANCE OF P-GLYCOPROTEIN-RELATED RESISTANCE IN PATIENTS WITH ACUTE LEUKEMIA

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Between 1989 and 1994 P-gp expression was prospectively studied in mononuclear bone marrow cells of 304 (221 AML; 83 ALL) acute leukemia patients. In 282 patients P-gp was investigated before and after therapy and in 22 patients only before therapy: 148 AML patients with AML-6 protocol (EORTC), containing daunorubicin, vincristine and conventional-dose cytarabine (ara-C), and 63 AML patients were treated with intermediate-dose ara-C plus amsacrine. Further 71 ALL patients were treated according to a German standard polychemotherapy protocol (BMFT04/1989). For AML patients with P-gp overexpression at primary diagnosis or early relapse/refractoriness, the predictive values for nonresponse to AML-6 protocol were 90% and 94% respectively, while late-relapsed AML patients with P-gp overexpression had a significantly ($P < 0.05$) lower predictive value of 73% for nonresponse. Additionally, in refractory and late-relapsed P-gp-overexpressing AML patients treated with intermediate-dose ara-C plus amsacrine the predictive values for nonresponse were 44% and 38%, respectively, significantly ($P < 0.05$) lower as compared to AML-6 protocol-treated refractory or late-relapsed AML patients. In P-gp-overexpressing treated ALL patients the predictive values of 50% and 55% for nonresponse were calculated at primary diagnosis and late relapse, respectively. P-gp overexpression is a common phenomenon in AML patients and has an inverse influence on AML-6 treatment outcome.

132 POSTER

MRP GENE EXPRESSION IN COLORECTAL CARCINOMAS

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To determine the clinically important mechanisms of multidrug resistance, we studied the expression of the MRP gene in primary colorectal carcinomas (N = 75). MRP RNA was determined by RT-PCR. MRP RNA was detected in 62 (83%) tumor specimens. The expression was independent of size and localization of the primary tumor, lymph node involvement, tumor stage and the survival durations of the patients. However, MRP gene expression correlated with MDR1 gene expression. In conclusion, the frequent expression of the MRP gene suggests its importance as a drug resistance gene in colorectal carcinomas. (Supported by Austrian Science Foundation.)

133 POSTER

EFFECT OF PACLITAXEL ON THE UPTAKE OF CIPROFLOXACIN AND OFLOXACIN BY HUMAN NEUTROPHILS

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Ciprofloxacin (CPLX) and ofloxacin (OFLX) are antimicrobial agents which concentrate and remain active within phagocytic cells. We have evaluated by a fluorometric assay the effect of paclitaxel in comparison with methotrexate, doxorubicin, Cis-platinum and etopoxide on the intracellular penetration of CPLX and OFLX in human neutrophils. The preincubation of cells for 30 min at 35°C with therapeutical concentrations of these antineoplastic agents yielded the following cellular to extracellular concentration ratio values (C/E) for CPLX and OFLX (at 20 min; 35°C; extracellular concentration: 5 mg/l).

		C/E	
Antineoplastic	**mg/l**	**CPLX**	**OFLX**
None		4.7 ± 1.2	4.6 ± 0.9
Paclitaxel	5	4.8 ± 1.0	4.3 ± 0.4
Methotrexate	10	5.1 ± 1.2	4.4 ± 0.7
Doxorubicin	1	14.3 ± 1.4	4.6 ± 1.1
Cis-Platinum	10	4.7 ± 1.6	3.7 ± 0.5
Etopoxide	10	5.5 ± 1.0	4.8 ± 1.3

Similar results were obtained when other extracellular concentrations of the antineoplastic agents were used. It is concluded that paclitaxel and the other drugs evaluated did not affect the intracellular penetration of quinolone antimicrobial agents.

134 POSTER

ENHANCED TUMOR RADIOIMMUNOTARGETING OF CHIMERIC ^{125}I-BR96-BIOTIN IN A SYNGENEIC RAT TUMOR MODEL USING WHOLE BLOOD EXTRACORPOREAL IMMUNOADSORPTION (ECIA)

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Chimeric BR 96 is a human IgG1 isotype with a high tumor selectivity for most human carcinomas of breast, lung, ovary, and gastrointestinal tract. The rapid internalization into tumor cells is another important feature for BR96. The aim of the study was to investigate if whole blood ECIA has an influence on tumor and normal tissue radioimmunotargeting.

Material and methods.: 30 BN-male rats inoculated intramuscularly (IM) and beneath liver- or kidney capsule (SR) with syngeneic rat colon carcinomas, expressing Ly Ag, were investigated. The rats were injected i.v. with 3.5–4.5 MBq of ^{125}I-BR96-biotin. ECIA of whole blood, using avidin-gel adsorption column, was performed 12 h after injection of Mab. *Results:* After completion of ECIA, whole body radioactivity was reduced by 48–62%, and plasma activity (%/g) by 85%. After finish of ECIA, the uptake in the liver-, SR-, and IM-tumors decreased by only 11, 23 and 13%, respectively, whereas the uptake in normal tissues was considerably diminished. T(umor)/bone marrow, T/liver, T/kidney and T/lung uptake ratios were enhanced in all 3 tumor models by a factor varying from 2.2 to 4.2. The uptake of Mab in Liver and IM-tumor was enhanced by increasing amount of Mab injected. *Conclusion:* ^{125}I-BR96-biotin proved high tumor-to-normal tissue ratios, which were even more enhanced by ECIA of whole blood.

135 POSTER

PHARMACOKINETICS AND PHARMACODYNAMICS OF TENIPOSIDE (VM26) COADMINISTERED WITH CYCLOSPORIN A (CSA) IN PATIENTS WITH METASTATIC RENAL CELL CANCER (RCC)

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Background: Chemosensitizers could alter the pharmacokinetics (PK) and pharmacodynamics (PD) of antineoplastic drugs. It was previously demonstrated that CsA modifies PK and PD of etoposide, an analog of VM26, but the effect of CsA on VM26 has not been clarified yet.

Methods: Thirteen patients with RCC in progression after standard therapy were accrued. Demographics: median age 61 years (range 44–75), male:female 9/4, median WHO P.S. 2 (range 1–3). The patients

received two courses of VM26 (200 mg/m^2/24 hrs i.v.) but no objective response was observed. Thus CsA (a loading dose of 5 mg/kg/2 hrs followed by 30 mg/kg/48 hrs i.v.) was added (VM26/CsA) and additional courses (1–5) were administered.

Results: A plateau concentration of CsA was obtained at the end of the loading dose: blood concentration was on average 2800 ng/ml (range 1745–3690 ng/ml), exceeding 2000 ng/ml (minimum effective level of CsA as a chemosensitizer) in all but one patient. CsA increased the area under curve (AUC) of VM26 in 9 out of 13 patients evaluated. On average the AUC of VM26 was increased by 45% after CsA administration ($P < 0.05$). Nadir granulocyte count was lower after VM26/CsA (average 1000/mmc, ranging from <100 to 2800/mmc) than after VM26 (average 2000/mmc, ranging from 200 to 5600/mmc). Hyperbilirubinemia was observed after VM26/CsA (average 3.2 mg/dl) while normal values were observed after VM26 (<1.5 mg/dl). Finally, after VM26/CsA one patient had a minor response at lung level.

Conclusion: This study indicates that CsA affects both PK and PD of VM26.

136 PUBLICATION

THROMBOXANE A2 AS A DETERMINANT OF SENSITIVITY TO PLATINUM AGENTS IN NON-SMALL CELL LUNG CANCER CELL LINES

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cis-Diamminedichloroplatinum (II) (CDDP) is one of most active anticancer agents for lung cancer. In this study, we evaluated the role of thromboxane A2 (TXA2), a metabolite of arachidonate, as a determinant of sensitivity to CDDP in non-small cell lung cancer (NSCLC) cell lines *in vitro* by using selective TXA2 receptor antagonists, S-1452 and BAYu3405. A-549, EBC-1, PC-3, and RERF-LC-MS cell lines which had been derived from human NSCLC were used for these experiments. Drug sensitivity tests were performed with MTT-assay. IC50 values for CDDP and an analogue (CBDCA) of these cell lines by 2-hour exposure were decreased by co-incubation with these TXA2 antagonists. Cellular accumulation of CDDP and CBDCA increased by S-1452. These results indicate the important role of endogenous TXA2 to modulate the cellular accumulation of the platinum agents and to determine intrinsic resistance to these agents in NSCLC cell lines.

137 PUBLICATION

THE EFFECT OF COMBINED TREATMENT, EPIRUBICIN (FREE/LOADED IN MICROSPHERES) AND/OR NIFEDIPINE, UPON THE EVOLUTION OF THE EHRLICH ASCITES TUMOR

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The effect of i.p. injected epirubicin-free or entrapped in gelatin microspheres with or without calcium channel inhibitor (nifedipine) on the development of Ehrlich ascites in mice was studied.

The experiments were carried out on 409 Swiss mice.

All animals were i.p. grafted with 1.5×10^6 tumor cells and divided into six groups: gr. I control; gr. II i.p. free epirubicin; gr. III i.p. epirubicin loaded microspheres; gr. IV i.p. free epirubicin + nifedipine; gr. V i.p. epirubicin loaded microspheres + nifedipine; gr. VI i.p. nifedipine.

Our results show statistically significant differences of the survival time between groups I, VI and groups II, III, IV, V. The less toxic effects were observed in groups treated with epirubicin loaded microspheres (III and V).

Our results demonstrate that epirubicin loaded microspheres alone or associated with nifedipine, improve the survival time and decrease the toxicity of the drug.

138 PUBLICATION

TOXICITY OF HIGH AND MEDIUM DOSES OF EPIRUBICIN

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The present analysis was carried out on seven EORTC multi-center trials, therefore provides basis for the evaluation of toxicity on a large number of patients, treated according to the same protocols. The aim of the study was to calculate the frequency of toxicity WHO grade 3 and 4, occurring during the treatment with Epi at doses of 90–150 mg/m^2. Frequency of toxicity was related to the level of initial and cumulative dose of Epi.

The analysis comprised 528 patients. Number of treatment cycles was 1–15; cumulative dose of Epi was 82.4–1354.8 mg/m^2. Leukopenia and alopecia occurred in 55% of treated patients, followed by nausea/vomiting −22%, anemia −13%, thrombocytopenia −12%, mucositis −11% and infectious 7%. These side effects, except infectious ones, correlated with the cumulative dose of Epi. Frequency of other toxicity was 2% or less.

Leucopenia, thrombocytopenia, anaemia, mucositis and nausea/vomiting occurred significantly more frequently in patients treated with Epi at a dose of 150 mg/m^2, compared with 90–110 mg/m^2 and fractionated doses.

Cardiotoxicity occurred in 2% of patients. However, it can not be ruled out that 7 deaths due to not well defined "cardiovascular disease" were directly connected with drug's cardiotoxicity and in that case, the cardiotoxicity would be 4% and the frequency of toxic deaths from this factor would be 3%.

139 PUBLICATION

A QUEST FOR OPTIMAL COMBINATION OF L-OHP, A NOVEL PLATINUM COMPLEX, WITH OTHER ANTICANCER AGENTS IN CANCER CHEMOTHERAPY *IN VITRO*

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In this *in vitro* study, the optimal conditions in combination were evaluated. An established human leukemia cell line (RPMI-8402) was target cells, and 15 kinds of anticancer agents were tested in combination with L-OHP. One agent in combination with L-OHP including control sample was evaluated in 18 kinds of different modalities. The cytocidal effects were assessed according to our evaluation method and were compared by taking OE ratio.

VCR, VDS and MCNU were not synergistically effective in any combination modalities. The remaining 12 agents showed synergistic effects but the effects were variably depending on the combination modality. Only 5-FU proved synergistic in any kinds of combination modality.

140 PUBLICATION

ANTHRACYCLINE ANTIBIOTICS ACCUMULATION IN TUMORS WITH CLASSIC AND ATYPICAL MULTIDRUG RESISTANCE (MDR)

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The typical MDR phenotype have been associated, among other signs, with reduced intracellular accumulation of MDR-causing drugs. We have studied the rubomicin (rub) and adriablastin (adr) accumulation by the fluorescent spectroscopy method. We have chosen, from our laboratory collection of P388 leukemia MDR-strains, vinblastine-resistant tumor (P388/vbl) possessed by MDR1 gene amplification and cross restistance to MDR causing drug and adriablastin-resistant tumor (P388/adr1) having incomplete pattern of cross resistance and no MDR1 gene amplification. There were moderate but constant differences in drugs accumulation between cells of sensitive and resistant strains. The rub and adr accumulation by P388/adr1 cells was 2.1 and 1.3 times less than that observed in sensitive cells. These finding were 1.7 and 1.3 for P388/vbl respectively. There were no differences of the parameter between resistant strains. Taken together the data suggest that several different mechanisms could participate even in case of classic MDR.