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.