Lübeck, Germany) was selected for MDR1 by exposure to actinomycin D. Using the parent line as negative control, the expression of MDR1-RNA and P-glycoprotein (P-gp) was confirmed by reverse polymerase chain reaction and immunohistochemistry, respectively. In the proliferation assay, marked resistance to DNR (>60-fold) was observed within the typical resistance pattern of MDR1. This was accompanied by reduced intracellullar DNR fluorescence as measured by flow cytometry. Several ways to circument AX resistance were then evaluated. (1) Addition of MDR1-revertants: both dexniguldipine (Byk Gulden, Konstanz, Germany) and dexverapamil (Knoll, Ludwigshafen, Germany) reduced resisance to DNR, with the former being more effective at equal concentrations. At non-toxic levels of the revertants, however, resistance was still severalfold. (2) Modification of AX chemistry: no cross-resistance to the 9-alkylated, 3'*N*-morpholinyl AX MX2 (Kirin Brewery, Tokyo, Japan) was observed. On the contrary, MX2 was 1.5 times more active in the MDR1 positive line than in the MDR1 negative parent line. Retained activity was accompanied by comparable fluorescence patterns in both cell lines. (3) Combination of (1) and (2): no further benefit was achieved by adding revertants to MX2. (4) Liposomal DNR: resistance against liposomally encapsulated DNR (DaunoXome, Vestar, San Dimas, USA) was still about 50-fold. (5) Use of non-AX non-MDR1 cytostatics: collateral sensitivity to cisplatin was observed (2.5 times more active in MDR1 positive cells). MDR1 may lead to enhanced vulnerability to some cytostatic agents, as shown here for MX2 and cisplatin.

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Novobiocin (Novo)-inhibitable VP-16 efflux in leukemia and ovarian carcinoma cells from patients

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Novo produced supra-additive cytotoxicity in combination with VP-16 in several tumor cell lines, including non-P-glycoprotein (P-gp) expressing multidrug resistant cell lines. The increase in VP-16 cytotoxicity by Novo was due to inhibition of VP-16 efflux through a yet unidentified membrane transporter, which is not shared by other drugs generally included in the multidrug resistant phenotype. To monitor the possible sensitivity of drug-resistant tumors to the combination of VP-16 and Novo in the clinical setting, in the present study 11 relatively pure tumor populations (>80% tumor cells) from patients with leukemia and ovarian carcinoma are analyzed. In six cases, Novo, in a range of from 150 to 1000 μM, progressively increased the intracellular accumulation of [^{3}H]VP-16 through inhibition of VP-16 efflux. In four of these six tumors, as well as in the five Novo-insensitive tumors, the P-gp was not detectable by flow cytometric analysis with MRK-16 and 4E3.16 monoclonal antibodies. The activity of Novo was not related to the expression of topoisomerase II in the individual tumors. A wide range of topoisomerase II levels were observed, with low expression of the enzyme possibly being implicated in drug resistance in at least one of the tumors analyzed. No MRP (multidrug resistance associated protein) expression was detected by Western blotting analyses of total cell lysates. For all of the cell lines analyzed in the laboratory to date, the increase in the intracellular accumulation of VP-16 induced by Novo has always been indicative of potentiation of the cytotoxicity of VP-16. It is therefore expected that the analysis of the effects of Novo on the accumulation of [^{3}H]VP-16 in clinical tumor samples will ultimately predict the anti-tumor potential of the combination in each individual patient. The preliminary finding that about 50% of clinical tumor samples analyzed are sensitive to the modulatory activity of Novo suggests that it may be possible to select a subgroup of patients which are most likely to benefit from this modulatory activity.

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Tumor type specific activity of cyclosporins as resistance modifiers *in vitro*

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The aim of the present study was to evaluate the ability of cyclosporin A (CsA) and its novel non-immunosuppressive derivative SDZ PSC 833 (PSC) to modify the response to doxorubicin and vincristine *in vitro*, in different hematological and solid human tumor types. Primary cultures of over 300 tumor samples, from patients with different hematological or solid tumors, were analyzed using the semiautomated fluorometric microculture cytotoxicity assay (FMCA). The resistance modifying activity of CsA and PSC in combination with doxorubicin and vincristine was evaluated in 12 groups of diagnoses. Some data on etoposide was included for comparison. Both cyclosporins showed resistance modifying activity in all hematological tumors tested, and in solid tumors activity was observed in ovarian carcinoma and childhood tumors. Little or no effect was found in the remaining tumor types, including breast, renal and adrenal cortical carcinomas and adult sarcomas. In most of the responsive cases the interaction between the modifier and the cytotoxic drug was synergistic. There was a tendency to higher activity in samples from previously treated patients, and an inverse relationship between degree of cytotoxic drug resistance and resis-