tance modifying activity was noted. No difference in potency between CsA and PSC could be discerned. The results indicate tumor type specific resistance modifying activity of cyclosporins *in vitro*. The results also suggest that treatment with resistance modifiers should be considered also for drug sensitive tumors in primary therapy. Drug resistance assays like the FMCA may become useful in preclinical evaluation of resistance modifiers.

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Inhibition of rhodamine-123 efflux and modulation of rhodamine-123 accumulation in CCRF VCR-1000 cells by dexniguldipine–HCl and other chemosensitizers

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Expression of P-glycoprotein (P-gp) in cell membranes of multidrug resistant cancer cells is a major cause for treatment failure in the clinical therapy of cancer. P-gp is an ATP-driven efflux pump for a variety of different cytostatic drugs and fluorescent dyes such as rhodamine-123, acridine dyes and others. Rhodamine-123 was used as a model substrate for P-gp mediated drug efflux in multidrug resistant and P-gp-positive CCRF VCR-1000 cells in serum free media. Accumulation of rhodamine-123 is reduced in CCRF VCR-1000 cells as compared to sensitive and P-gp-negative control CCRF-CEM cells. Dexniguldipine–HCl blocked P-gp mediated rhodamine-123 efflux and increased intracellular rhodamine-123 content dose dependently. In accumulation studies a half-maximal increase in cellular rhodamine-123 content was seen at a dexniguldipine–HCl concentration of 0.2 μmol/l. SDZ PSC 833, amiodarone and cyclosporin A were of similar potency, while verapamil, dipyridamole and quinidine were less active. The maximum level of chemosensitization with amiodarone was clearly below the levels seen with the other modulators. In addition to these equilibrium accumulation studies, rhodamine-123 efflux was measured in the absence or presence of 1 μmol/l, 10 μmol/l and 100 μmol/l of chemosensitizers. In these efflux studies all chemosensitizers decreased rhodamine-123 efflux and concomitantly increased half-life time of cellular rhodamine-123 content dose dependently. In the absence of compounds rhodamine-123 half-life times of a few minutes were observed in resistant CCRF VCR-1000 cells. In the presence of chemosensitizers half-life times were increased to several hours at high concentrations of compounds. At a concentration of 1 μmol/l, dexniguldipine–HCl and SDZ PSC 833 showed the highest potency, while amiodarone, quinidine and verapamil were less effective. Amiodarone, although used at saturating concentrations, showed only weak potency of chemomodulation in these efflux studies. This may indicate a different mode of action for amiodarone in comparison to the other compounds.

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Nuclear changes associated with MDR reversal *in vitro* by S9788 in human leukemic cells

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The development of effective means to circumvent multidrug resistance in the clinical setting would provide a major advance in the successful treatment of cancer. A variety of compounds have now been identified that are capable of reversing the MDR phenotype in drug-resistant cells, e.g. verapamil, quinidine, cyclosporine. Among these, the triazinoaminopiperidine derivative S9788 is a new multidrug resistance modulator, active *in vitro* and *in vivo* on various tumors.[1] Recently, we showed specific morphologic alterations in nuclei from human tumor cells resistant to chemotherapy by a typical MDR mechanism.[2] The aim of this work was to evaluate the effects of S9788 on these cytological changes observed in human MDR leukemic CEM and K562 cell sublines. Vinblastin sensitive and resistant CEM cells and doxorubicin sensitive and resistant 562 cells were cultured in the presence or absence of verapamil (5 μM), S9788 (5 μM) or both (2.5 μM + 2.5 μM). Using MTT cytotoxicity assay, S9788 displayed a greater reversing activity than verapamil. Neither drug significantly affected sensitive cell survival. Quantitative cytological analysis was performed on Feulgen-stained cell smears by image cytometry; 21 parameters were computed on each nuclear image. The different modulators displayed only few or non-significant effects on the morphology of sensitive cells. On resistant cells, S9788 and the combination S9788-verapamil, but not verapamil alone, induced significant cytological variations, although all drug treatments resulted in a significant resistance reversal. These modifications were characterized by a partial reversion of some parameters (more specifically nuclear textural parameters) to values closer to those observed in parental sensitive cells. In conclusion, within the CEM or K562 cell lines, reversal of drug resistance by S9788 is associated with significant cytological changes. These results could shed new light on S9788 activity, suggesting a complex action on cell metabolisms rather than a restricted action on drug efflux alone.

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