Differential Modulation of P-Glycoprotein, the Multidrug Resistance Mediator, by Cremophor in Normal Versus Leukemic Hematopoietic Cells

To the Editor:

Multidrug resistance (MDR) caused by the expression of the transmembrane efflux pump P-glycoprotein (Pgp) has been suggested to limit the effectiveness of chemotherapy in acute myeloid leukemia (AML) patients by lowering the intracellular concentrations of various cytotoxic agents, including anthracyclines, vinca alkaloids, and etoposide. Attempts to revert MDR in vivo, to date, have been hampered by the severe side effects of currently available Pgp modulators such as verapamil and cyclosporine A. PSC 833, a nonimmunosuppressant and nonnephrotoxic analog of cyclosporine with significantly greater efficacy in inhibiting Pgp, is currently under development as a modulator of MDR in the clinic.

PSC 833, like cyclosporine, is administered in a Cremophor EL (CEL) (Sigma Diagnostics, St Louis, MO) based solution. CEL, a nontoxic solubilizing polyethoxylated castor oil, itself has been shown to exert MDR modifying activity at in vitro concentrations achievable in vivo when tested against malignant hematopoietic cell lines or isolated blast cells from patients with AML. To date, CEL has not been tested for inhibition of Pgp function in normal Pgp expressing hematopoietic cells, whereas cyclosporine and PSC 833 showed equal potency in inhibiting Pgp in normal natural killer cells as in leukemic cells.

We evaluated the effects of PSC 833 (dissolved in ethanol and added to a final concentration of 1 μmol/L (provided by Sandoz Pharmaceutical Co, East Hanover, NJ) and CEL (0.2%) on Pgp function as reflected by inhibition of rhodamine123 (Rh123) efflux in 10 patients with AML and in seven healthy individuals. By immunophenotyping, done as described previously, four patients typed as differentiated acute myeloid leukemia, and three each typed as acute myelomonocytic leukemia or acute monocytic leukemia. In all cases, the immunologic diagnosis of AML was consistent with cytologic features. Because CD34 expression is correlated with classical Pgp function, Rh123 efflux was monitored in CD34+ gated blast cells, as previously described, or in CD3+ peripheral blood T lymphocytes, which demonstrated Pgp expression in 40% to 60% of cells when measured by staining with antibody 4E3. (provided by Dr R. Arceci, Cincinnati, OH), in agreement with previous data using UIC2 as anti-Pgp antibody. Of the leukemic cells, 5% to 97% expressed Pgp by antibody staining. When AML blast cells or peripheral blood mononuclear cells loaded with Rh123 were incubated at 37°C in the absence of Pgp inhibitors, 8% to 74% of AML blasts (median 36%) and 16% to 33% of CD3+ lymphocytes (median 24%) became Rh123-dull within 1 hour, whereas virtually 100% of either cell type remained Rh123-bright if maintained at 4°C. When the incubation at 37°C was performed in the presence of PSC 833, dye efflux was inhibited between 68% and 99% in AML blasts (median 91%) and 76% to 100% in CD3+ lymphocytes (median 99%). On the other hand, with CEL as the Pgp modulator, while Rh123 efflux from AML blasts was consistently inhibited (21% to 100%, median 88%), dye efflux from CD3+ lymphocytes was unaffected or potentiated. Increasing the concentration of CEL from 0.2% to 0.4%, 1%, and 2% did not result in Rh123 efflux inhibition in the lymphocyte population, thereby excluding the possibility that higher doses of CEL might be necessary to interfere with the function of a potentially higher density of Pgp molecules in the membrane of lymphocytes than in AML blast cells.

Direct interaction through binding to Pgp or a change in intracellular drug localization is the presumed mechanism of action of many resistance modifiers, including PSC 833. However, inhibition of Pgp by surfactants, such as CEL, may be caused by perturbation of membrane structures. Although there are data on intracellular drug redistribution in the presence of CEL, the results of others are compatible with the hypothesis that the binding and transport capabilities of Pgp may be impaired by CEL because of disruption of the cell membrane. Whatever its mechanism of action, our data suggest that Pgp function is less susceptible to CEL than Pgp in leukemic myeloid cells. Whether this discrimination is actually related to a structural difference in Pgp in the two cell types or to the different composition of the cell membrane in lymphoid versus myeloid cells remains
presently unclear. However, a selective inhibition of Pgp in malignant cells while sparing the normal physiologic activity of this drug pump in normal tissues is of potential clinical significance: eg, when considering the potent effects of Pgp modulators such as PSC 833 on natural killer cell activity. Although CEL is currently unique with its potent but selective Pgp inhibition in leukemic cells, the possibility of targeted Pgp modulation should be further explored in the development of novel Pgp modulators.

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REFERENCES

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