Editorial

Modulating Multidrug Resistance: Can We Target this Therapy?1

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The Multidrug Resistant Phenotype

The MDR phenotype was developed by exposing cells to very high concentrations of cytotoxic agents in vitro (1). The best understood mechanism of resistance in MDR is the increased expression of P-gp, a transmembrane energy-dependent drug efflux pump, which is most efficient at transporting natural occurring substances such as the anthracyclines, Vinca alkaloids, taxanes, and epipodophyllotoxins (2). P-gp is encoded by mdr1, one of two genes found in humans that belong to a multigene family designated mdr. These genes are members of a superfamily of ABC transporters that share a high degree of homology with a large number of both prokaryotic and eukaryotic membrane transport proteins (3). Other ABC transport proteins that have been implicated in MDR include the MRP-associated proteins (MRP1–5), the lung resistance protein (LRP), and the breast cancer resistance protein. Tumors may coexpress several of these transport proteins.

In normal tissues, P-gp is frequently present along the apical border of a variety of secretory epithelia and is involved in the excretion of toxins, and the transport of ATP, chloride ions, steroids, and polypeptides that lack a signal leader sequence (4, 5). P-gp also plays an important role in the establishment of important biological barriers, such as the placenta, the blood-brain, and the blood-testes barriers (6, 7). In addition to P-gp, transporters in the ABC superfamily located in the liver and intestine that contribute to the bioavailability of p.o. administered agents include the canalicular multispecific organic anion transporter (MRP2) and the bile salt export pump (8, 9).

In MDR cell lines that express P-gp, there is significant variability in the cross-resistance pattern to chemotherapy. Differences in the level of P-gp expressed on the plasma membrane, altered genetic regulation, or post-translational modifications of P-gp may contribute to this heterogeneity. For example, point mutations within the mdr1 gene may produce P-gps having 4-fold differences in affinity for agents such as vinblastine (10, 11). Differences in the phosphorylation status of P-gp affect the efficiency of this energy-dependent transporter, and other post-translational modifications may also occur.

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3 The abbreviations used are: MDR, multidrug resistant; P-gp, P-glycoprotein; ABC, ATP-binding cassette.

Clinical Experience in Modulation of MDR

The drugs selected for the initial clinical studies were ones already approved for clinical use, and verapamil, cyclosporin, tamoxifen, and quinidine were the agents most frequently evaluated. Plasma concentrations equivalent to the concentrations necessary to inhibit drug efflux in vitro were difficult or impossible to achieve with these drugs because of toxicity, although conceivably the necessary concentrations may have been reached in tissue despite inadequate plasma levels, because these were highly lipophilic drugs. Early on, it became clear that reversing the resistance of malignancies like renal cell cancer and colorectal cancer would not be possible, despite high levels of expression of P-gp in these tumors. This focused the evaluation on tumor histologies that were frequently sensitive to anthracyclines, Vinca alkaloids, and taxanes initially, and in which the expression of MDR was shown in correlative studies to be associated with an inferior prognosis. Even in this setting, testing the hypothesis that modulators can restore sensitivity to chemotherapy has been difficult. Studies that evaluated modulators in patient populations with extensive previous therapy rarely registered a response, presumably because resistance in these patients was multifactorial and blockade of drug efflux, even if successful, was inadequate to sensitize the tumor. It also became clear that modulators block normal excretory function and delay clearance of chemotherapy. This resulted in a 30–350% increase in the area under the drug concentration-time curve.

The limitation of the potency of the modulators has been addressed by the development of compounds that are less toxic and more effective as inhibitors. These second generation modulators include the cyclosporin analogue PSC388 and novel agents such as the amido-keto-pipecolinate VX-710. Plasma concentrations exceeding the concentrations required to block drug efflux in vitro are readily achievable in humans. These newer agents have additional advantages. Some, like the difluorocyclopropyl dibenzosuberase LY335979, have less impact on the pharmacokinetics of chemotherapy drugs (16), and others, like VX-710, also have activity in modulating efflux proteins like MRP-1 rather than P-gp only (17). In this issue of Clinical Cancer Research.
Cancer Research, Toppmeyer et al. (18) describe a well-designed study evaluating the activity of VX-710 and paclitaxel in a group of patients with breast cancer insensitive to paclitaxel alone. Breast cancer is a disease in which the overexpression of P-gp has been associated with a poor response to chemotherapy (19). Recognizing the impact that VX-710 would have on drug clearance, the dose of paclitaxel selected in this study was 80 mg/m², which produced an area under the drug concentration-time curve and critical threshold dose comparable with a dose of 175 mg/m², which is in the therapeutic dose range of paclitaxel. The toxicities recorded in the study confirmed that the maximal dose of paclitaxel had been selected. The activity observed was limited, contributed to premature termination of the study, and confirmed that in unselected patients with resistant disease the combination of a modulator and a cytotoxic drug will be effective in only a small subset of patients. The final results of a number of phase III studies that tested second generation modulators in patient populations less heavily exposed to previous chemotherapy than the patients included in the Toppmeyer study are pending, but the preliminary reports, at least in leukemia, have not been encouraging. The available data do not preclude the possibility that there may be some tumor histologies in which the early introduction of a modulator prevents overgrowth of a subset of intrinsically resistant clones or suppresses the acquisition of the MDR phenotype and resistance to chemotherapy (20). More likely, the data indicate that greater sophistication in the selection of patients appropriate for treatment with a modulator is necessary.

Identifying the ideal patient for this treatment strategy would require knowledge that the MDR phenotype was present, that other mechanisms of resistance were limited, and that the modulator inhibited efflux of the chemotherapy it was paired with. Establishing the presence of the MDR phenotype is not trivial; however, given the array of drug efflux proteins that may be expressed in MDR, potential differences in transporter activity of the expressed proteins, and differences in the affinity of these proteins for the substrate and modulator selected. A functional assessment of whether intracellular drug retention was improved with the addition of the modulator would be more informative than a biochemical characterization. Determination of the effect that a modulator has on intracellular retention of a fluorescent substrate transported by MDR proteins is possible by flow cytometry for patients with malignancies that can be sampled from the bone marrow or peripheral blood. Assessment of drug efflux in solid tumors is also feasible with 99-Tc-sestamibi imaging (Fig. 1), a Food and Drug Administration-approved radiopharmaceutical that is both a substrate for P-gp and to a lesser extent MRP-1 (21). In breast cancer, efflux rates of 99-Tc-sestamibi correlated well with biochemical assessment of P-gp and response rates to neoadjuvant chemotherapy (22, 23). Uptake and retention of 99-Tc-sestamibi is enhanced for patients treated with modulators of MDR, including VX-710. Clinical studies that selected patients based on a functional demonstration of efflux inhibition by the modulator that is tested have yet to be conducted.

Given the accelerating array of promising agents targeting diverse biological pathways that are being introduced into the clinic, should continued effort be invested in developing MDR modulators? Several scenarios can be envisioned. Studies of the second generation modulators in early disease and in patients selected on the basis of functional studies should be helpful in defining whether overcoming drug efflux in tumors produces meaningful clinical benefit. Another approach is to use these newer, less toxic modulators to overcome normal physiological barriers in the central nervous system and in the intestine. Many of the new targeted therapies are putatively cytostatic agents and require continuous exposure. However, the oral route is precluded for a number of these compounds because of poor or no oral bioavailability. The coadministration of modulators that block intestinal efflux and metabolism by P450 enzymes may permit the oral administration of otherwise poorly absorbed drugs. For example, the oral absorption of paclitaxel was increased 10-fold when combined with PSC833 in a murine model (24). Enhanced oral absorption of peptides and peptidomimetics has also been demonstrated (25).

A dozen years ago, the potential of sensitizing resistant tumors to chemotherapy by adding a modulator of drug efflux captured the attention of the clinical oncology community. Currently, “targeted therapies” has replaced MDR as a primary area of interest. It remains possible that suppression of the induction of MDR or inhibition of normal physiological function will result in clinically meaningful higher concentrations of chemotherapy in a tumor, the central nervous system, or absorbed through the gastrointestinal tract. As a result, continued development of agents like VX-710, which are more potent and less toxic inhibitors of MDR, remains a worthy goal. The challenge will be how to best target this approach.

References
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