Chemotherapy Resistance in Acute Leukemia

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ABSTRACT

Drug resistance markers are often predictive of treatment response and outcome in patients with acute myeloid leukemia. The immunologic detection of drug efflux pumps such as P-glycoprotein (Pgp) and multidrug resistance associated protein 1 (MRP1) correlate with functional assays of drug resistance and these drug accumulation defects also appear operable in ALL. Other markers such as LRP, bcl-2, and BRCP, have been described in patients with AML although their pathophysiology and clinical relevance is less clear and methodology for their quantification not well standardized.

Preclinical studies have shown that small molecules capable of reversing efflux can restore drug sensitivity in resistant tumor models. While initial clinical studies were limited by both potency and specificity of the reverser, later studies with more effective reversers have in many instances been limited by pharmacokinetic interactions exacerbating the clinical toxicities of chemotherapy. Nonetheless, one large randomized study using cyclosporine has demonstrated a proven survival advantage without increased toxicity, although the inconsistent results with other modulators raises doubt as to the utility and overall strategy of using drug efflux blockers in patients with established Pgp overexpression. Most of these patients have additional mechanisms of resistance and achieving meaningful clinical responses will likely require more complex clinical strategies. Preventing or delaying development of drug resistance in chemosensitive patients represents another therapeutic strategy to be tested.

Key Words: Acute Leukemia, resistance, Pgp, MRP1.

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Cellular mechanisms of drug resistance have been increasingly better defined for patients with acute leukemia and other hematologic malignancies. The best characterized resistance profile is the phenotype of multidrug-resistance (MDR) mediated by P-glycoprotein (Pgp). Pgp is a transmembrane glycoprotein conferring cross-resistance to a variety of mechanistically and structurally unrelated cytotoxic drugs such as anthracyclines, taxanes, vinca alkaloids, and epipodophyllotoxins[1,2]. All anthracyclines are subject to Pgp-mediated resistance, despite some evidence that idarubicin has greater cellular retention and is less susceptible to Pgp-mediated efflux[3,4]. In patients with AML, Pgp expression correlates with poorer outcome and also occurs with increasing frequency in those patients with more advanced disease.

Pgp is a member of the ATP binding cassette (ABC) gene superfamily which is conserved throughout species evolution[1,2,5-7]. ABC transporters are involved in a diverse range of transport functions ranging from the epithelial transporter mutated in cystic fibrosis (CTFR), the canalicular multi-specific organic anion (cMOAT) and canalicular bile acid (cBAT) transporters of liver, monocyte secretion of IL-1ß (ABC1), antigen processing in T-cells (TAP), cholesterol and phospholipid efflux (ABCA1), and non-Pgp mediated anthracycline transport initially described in breast cancer cell lines (BCRP) and also known as the mitoxantrone resistance gene (MXR)[8,9]. Their phylogenetic conservation suggests a broad role in protection from naturally occurring toxic compounds (xenobiotics). In mammalian species, the systemic elimination of xenobiotics by the liver and kidney, the integrity of the blood-brain barrier, the isolation of germ cells from the systemic circulation, and protection of the stem cell compartment are all likely mediated in part by ABC transporters.

Studies from different investigators using both flow cytometry and functional efflux assays have demonstrated that AML patients with blasts that express Pgp do worse than Pgp negative patients[10,11,12] with a progressive increase in Pgp expression with advancing age and significant correlation of Pgp expression with decreasing CR rate and increasing incidence of resistant disease[12]. Increases in Pgp expression at relapse may account for differences in sensitivity to daunomycin in patients with acute promyelocytic leukemia at presentation and first relapse[13]. Most studies confirm strong correlation between phenotypic Pgp expression and functional efflux, while the Southwest Oncology Group has also shown a small but consistent blast population with discordance between functional and structural profiles in that some cells show efflux resistant to cyclosporine and no phenotypic evidence of Pgp expression[11], a phenomena also suggested by other investigators[14,15]. This profile may represent expression of an alternate ABC transporter, although the prognostic impact of this resistance profile is not yet characterized.

A small study evaluating breast cancer resistance protein (BCRP) in AML patients showed a broad range of expression and poor correlation with Pgp expression[15,16]. Inasmuch as the resistance spectrum of anticancer drugs for BCRP is similar to Pgp, this may represent another clinically significant ABC transporter in patients with acute leukemia, and BRCP may account for some of the non-Pgp cyclosporine resistant efflux described[11].

Patients with adult ALL have not been as well characterized but have been shown to have a relatively high incidence of phenotypic Pgp expression[17-19] with variable prognostic implications. A recent study has demonstrated high Pgp expression along with strong concordance of phenotypic Pgp with increased functional efflux[17]. Of interest, this study confirmed the discrepant finding of immunologically undetectable Pgp in cells with cyclosporine reversible efflux, suggesting alternate membrane transporters as previously described in clinical AML samples.

Lung resistance protein (LRP) was initially identified in a lung cancer cell line during in vitro selection for drug resistance[20-23]. It has significant homology with rodent vault proteins which are subcellular organelles likely involved in nuclear-cytoplasmic transport. Enforced expression of LRP in transfection experiments is not sufficient to confer resistance, suggesting other cofactors or

posttranslational assembly is necessary for biological function[20]. Of interest, LRP expression was increased in patients with AML at relapse following response to an induction therapy that included cyclosporine to overcome Pgp resistance[23], suggesting that modulating Pgp-mediated resistance may result in selection or upregulation of LRP as a secondary resistance mechanism after Pgp reversal. In several series, LRP expression in AML has been shown to be more predictive than Pgp in terms of CR rates, resistant disease and overall survival[21,23,24], although this has not been a consistent finding[11,25], perhaps attributable to variation in assay techniques[26].

Multidrug resistance associated protein (MRP) is another member of the ABC superfamily family and is capable of efflux and intracellular sequestration, in conjunction with GSH conjugation or cotransport[10,27]. The substrate specificity of MRP is similar but more limited than Pgp, and its normal physiologic role may be detoxification of intracellular oxidants. In a large SWOG study, MRP was expressed at relatively low levels and decreased with advancing age, although neither MRP1 nor LRP detection provided any clinically significant prognostic value[11]. While some studies confirm MRP's lack of prognostic utility[24,27], others have shown that MRP detection is predictive of outcome and adds prognostic value to Pgp for both complete remission rates, relapse-free, and overall survival for patients expressing both phenotypes[10]. These discrepancies may be attributable to the different size populations tested or to methodologic differences with SWOG assessing MRP-specific efflux after glutathione depletion and others using efflux inhibition by probenecid and alternate fluorescent substrates.

Topoisomerase II is the cellular target of anthracyclines and epipodophyllotoxins and decreased levels of topoisomerase IIa correlates with decreased sensitivity to these agents[28,29]. In vitro selection of resistant mutants in the presence of Pgp reversing agents can lead to resistance mediated in part by lower protein levels and functional activity of topoisomerase II[30-32]. In a small series of patients with relapsed AML treated sequentially with topotecan (a topoisomerase I inhibitor) followed by mitoxantrone and etoposide, levels of topoisomerase IIa correlated with outcome[33]. In this pilot study, patients with induction of higher topoisomerase IIa levels had better responses than those without, in accord with preclinical data suggesting that down regulation of topoisomerase II confers relative resistance to therapy that targets topoisomerase II. Assessment of topoisomerase II quantity and activity as well as correlation with clinical outcome can be complicated since topoisomerase activity in cell cultures can vary by growth phase and cell cycle status while quantitative assessment of clinical samples can show marked heterogeneity within each specimen's blast population[34].

Cytarabine-mediated drug resistance has classically been characterized by decreased levels by deoxycytidine kinase (dCK) which metabolizes cytarabine to the active triphosphate substrate, as well as increased levels of cytidine deaminase (CDD) which catabolizes the active compound. Alternatively, efflux mediated resistance has been demonstrated in preclinical studies[35]. Since cytarabine at various doses has a central role in most AML therapies, these resistance mechanisms could prove to have clinical significance. The literature evaluating ara-C resistance is not as substantial as other resistance mechanisms. One study showed good correlation of cytarabine resistance in clinical AML samples from older age patients and those with secondary onset[36]. Another pilot study examining cytidine deaminase (CDD) in clinical samples showed significantly lower CDD activity in untreated and responding patients, than those with refractory disease[37].

Overexpression of bcl-2 and other apoptosis pathway regulatory genes such as bcl-xl have been associated with drug resistance in leukemia cell lines[38] although correlation with outcome in clinical samples has been inconsistent[39].

CLINICAL TRIALS WITH DRUG RESISTANCE MODIFIERS

Encouraged by preclinical evidence that small molecules can overcome drug resistance in cell culture, rodent xenografts, and transgenic murine

models, clinical trials have tested whether Pgp efflux reversers can improve outcome in AML patients with high Pgp expression. Initial trials utilizing drugs such as verapamil and quinine showed limited efficacy as side effects from these compounds did not allow adequate serum levels to reverse Pgp. Because many Pgp blockers affect the pharmacokinetics of anticancer drug excretion by the kidney and liver, and in some instances compete for hepatic metabolic pathways such as the P450 system, it has typically been necessary to reduce the dose of chemotherapy during concurrent therapy with Pgp blockers to achieve a comparative regimen of equivalent clinical toxicity. To accommodate these effects, many phase I and II trials were designed to establish regimens equitoxic to similar regimens without the Pgp reverting drug. Of the initial drugs tested, cyclosporine showed the highest Pgp reversing activity and the most promising therapeutic index.

Using cyclosporine, a phase I-II study in patients with relapsed and refractory AML demonstrated clinical utility in terms of a response rate greater than expected based on historical reference, remission "inversions" with clinical remission durations longer than with prior regimens, and absence or decrease of mdr1 expression in leukemia specimens at later relapse[40]. Based on the encouraging results from this pilot study, a comparative phase III study in the same type of patient population was recently completed. All patients received daunorubicin by continuous infusion (45 mg/M^2/day x 3) followed by high-dose cytarabine (3 gm/M^2/ day x 5) with half also receiving cyclosporine (16 mg/kg/day) concurrent with the daunorubicin infusion. Although daunomycin dose was not reduced on the cyclosporine arm, toxicities were equivalent except for reversible hyperbilirubinemia in those patients receiving cyclosporine. Patients receiving cyclosporine had a lower rate of resistant disease and improvement in progression-free and overall survival at both 2 and 3 year analyses[41]. An identical regimen in patients with myeloid blast crisis of CML did not show any benefit for the addition of cyclosporine[42].

In contrast, similar trials using cyclosporine in high risk AML conducted by the Medical Research Council (MRC)[43] and Eastern Cooperative Oncology Group (ECOG)[44] in adults treated with daunomycin, etoposide and cytarabine in conventional pulse doses, showed no benefit from the addition of cyclosporine. Another single arm study in children with high-risk AML by the Children's Cooperative Group and Pediatric Oncology Group (CCG/POG)[45] using mitoxantrone, etoposide, and cyclosporine showed no benefit compared to historical controls. Differences in trial design, study population, and dosing may account for these conflicting results. The MRC study used a lower cyclosporine dose that does not consistently lead to serum levels adequate for reversing Pgp, while the MRC, ECOG, and CCG/POG studies gave cytotoxic drugs by conventional pulse administration, leading to greater peak pharmacokinetic (PK) effects and likely exacerbating clinical toxicity. The MRC, ECOG, and CCG/POG studies also used etoposide which is likely a poorer Pgp substrate, and potentially less effective than daunomycin and cytarabine in AML, so that in the presence of cyclosporine's PK effects, etoposide may contribute relatively more to clinical toxicity than efficacy.

PSC833 (valspodar, Amdrey) is a cyclosporine analog with significantly more in vitro Pgp reverting activity than cyclosporine and a comparative lack of immunosuppressive or nephrotoxic activities. PSC833 retains cyclosporine's pharmacokinetic effects with inhibition of the metabolism and excretion of anticancer drugs such as anthracyclines and epipodophyllotoxins. Clinical data has shown increased intracellular daunomycin in leukemic blasts expressing Pgp during in vivo PSC833 exposure[46]. A number of phase I-II studies were performed in AML patients with high Pgp expression using PSC833. For older patients with newly diagnosed AML as well as those with relapsed and refractory disease, dose reduction of anticancer therapy was necessary with concurrent PSC833, to obtain regimens of equivalent toxicity[47-49]. Dose reduction ratios were similar from study to study with absolute reduction dependent on the population studied and the relative dose-intensity of each regimen tested. Unfortunately, when many of these regimens were evalu-

ated in phase III comparative studies, clinical outcomes were not improved. In older patients with newly-diagnosed AML, one study was stopped early because of excessive toxicity in the PSC833 group despite attenuated doses of daunorubicin[50], while another appears to show no significant improvement in patients receiving PSC833 on final evaluation. Other studies looking at patients with relapsed and refractory AML have shown no convincing efficacy for PSC833[51].

The use of Pgp reversing compounds possessing significant pharmacokinetic effects on concomitant anticancer therapy make clinical trials both difficult to perform and difficult to analyze. The successful SWOG study with cyclosporine[41] used a schedule and consolidation schema distinct from the other regimens. Whether continuous infusion daunomycin along with cyclosporine was particularly advantageous, perhaps acting in synergy with high-dose ara-C in the relapsed/refractory population, or whether cyclosporine and not PSC833, affects other transporters or has other biological effects leading to improved outcome, are critical speculative issues without current resolution. Pgp reversers without pharmacokinetic effects have been developed and are being tested in clinical trials[52].

Alternatively, targeting populations with established Pgp expression may not be the most efficacious approach for any Pgp reversing agent. Pgp expression may be representative of evolution or selection of other mechanisms of drug resistance[25], whether induced or selected by prior chemotherapy[53], or as a natural evolution of the leukemic process. Studies suggesting the additive prognostic value of multiple resistance markers support this concept[10,54]. Furthermore, preclinical data suggests that Pgp reversers can suppress emergence of resistance[30-32] while other studies show that Pgp expression can occur rapidly after exposure to cytotoxic therapy. One study demonstrated increased Pgp expression and function in clinical samples within hours of ex vivo exposure to cytotoxic agents[55], while another in metastatic sarcoma patients showed evidence that in vivo Pgp gene expression is rapidly inducible within minutes of treatment[56]. Using Pgp blocking agents in patients without Pgp expression or other resistance mechanisms is an alternate strategy that is currently being pursued in a large clinical trial[57].

CONCLUSION

Of the better characterized markers of drug resistance in AML, phenotypic and functional Pgp expression predicts outcome more consistently than LRP and MRP, although the prognostic utility of these and other resistance markers may change with larger studies and more consistent methodology. Despite preclinical experiments showing that some resistant phenotypes can be overcome with reversing agents, the cellular “resistance profile” likely represents a complex interaction of multiple cellular alterations, with mutations leading to drug resistance also conferring other biological advantages. As such, overcoming clinical resistance in leukemia therapy may require not only targeted resistance modifiers, but a more complete biological and clinical understanding of the leukemic process.

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