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Reversal of Multidrug Resistance in Acute Myeloid Leukaemia and Other Haematological Malignancies

P. Sonneveld

University Hospital Rotterdam-Dijkzigt, Department of Haematology, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

INTRODUCTION

THE CLINICAL course of many malignant haematological tumours, such as acute myeloid leukaemia (AML), multiple myeloma (MM) and Non-Hodgkin's lymphoma (NHL), is characterised by initial responses in the majority of the patients, while later at relapse the presence of resistant tumour cells leads to refractory disease. Goldie and Coldman have hypothesised that small clones of resistant cells are present at diagnosis or may develop through spontaneous mutations. These cells expand by selection during treatment and later these overgrow the sensitive cells [1]. A major tool for investigating the mechanisms of resistance is the development of resistant cell lines by exposing cells *in vitro* to increasing drug concentrations. Such studies have identified the existence of so-called pleiotropic drug resistance (multidrug resistance (MDR)) [2, 3]. In this overview, the pharmacological approaches to reverse the MDR phenotype in AML and other haematological diseases will be summarised and several relevant studies will be discussed.

MULTIDRUG RESISTANCE

A major limitation for success in cancer chemotherapy is the growth of a drug-resistant subpopulation of cells. These subpopulations of cells are usually cross-resistant to a spectrum of cytotoxic compounds of natural origin, such as anthracyclines (doxorubicin, daunorubicin), vinca alkaloids (vincristine, vinblastine), epipodophyllotoxins (etoposide, teniposide), taxanes and amsacrine. These drugs share few structural and functional similarities except for the fact that they are small, biplanar and hydrophobic molecules. They enter the cell by passive diffusion across the cell membrane lipid bilayer. Alkylating agents, cisplatin and antimetabolites do not share these characteristics. Phenotypic characteristics of independently derived MDR cell lines are remarkably similar, despite their tissue origin and the *in vitro* protocols used for their selection [4, 5]. The most striking phenotypic marker of MDR is the overexpression of a membrane protein which is designated P-glycoprotein (Pgp). Pgp belongs to a group of phosphorylated glycoproteins first described in hamster ovary cells. The classical form of MDR was established when in a large range of cell lines similar increased Pgp expression was found [6]. In patients, primary or required resistance to chemotherapy is also associated with the expression of Pgp. In addition, there are several other proteins that are responsible for a form of pleiotropic resistance as shown in multidrug-resistant cell lines that do not express Pgp, but do express the multidrug-resistance related protein (MRP).

MDR1 EXPRESSION IN HAEMATOLOGICAL MALIGNANCIES

MDR1 expression has been demonstrated in many solid and haematological malignancies [7], particularly tumours derived from tissues that normally express *MDR1* [2, 8]. Tumours derived from the haematological compartment that frequently express *MDR1* include acute and chronic leukaemia and lymphoma [9–16]. High *MDR1* expression is more frequently found in tumours of patients that have previously been treated with natural product cytostatic drugs [2]. This suggests that *MDR1* expression can be induced by selection through exposure to these drugs. Several anticancer agents may be involved in the activation of *MDR1* transcription [17, 18]

AML is a clonal disease which originates from clonal transformation of an (undifferentiated) stem cell. This may explain why expression of *MDR1* is frequently observed in blast cells from *de novo* AML (Table 1). Several studies have found *MDR1* expression in untreated AML blast cells. The number of patients with *MDR1* expression varied from 19 to 75% of untreated AML cases [19–31] and high risk myelodysplasia [32]. The variable number of positive samples between these studies may, at least partly, be explained by the difference in analytical assays used for *MDR1* analysis. Some studies have also investigated *MDR1* expression in relapse AML. Generally, patients with refractory and/or relapse AML more frequently express *MDR1* than *de novo* patients [20, 23].

Several assay methods of *MDR1* expression are available for evaluation of clinical samples, but which do not necessarily produce comparable results (Table 2). Generally, bulk methods such as mRNA–PCR or Northern blot do not recognise quantitative differences of *MDR1* expression in subpopulations of cells with a certain morphology, and the results may be influenced by contaminating T-cells. It is not possible with these assays to correlate *MDR1* expression with maturation and/or differentiation markers. Therefore, most investigators prefer to determine *MDR1* expression at the protein level (P-glycoprotein). Pgp-specific antibodies, such as C219 and

Table 1. Clinical significance of multidrug resistance in de novo *AML*

[Ref.]	MDR assay*	MDR expression (%)	Patients (*n*)	Prognostic value for response (CR)
[19]	*MDR1* mRNA	67	15	Yes, $P = 0.01$
[22]	*MDR1* mRNA	71	63	Yes, $P = 0$
[21]	*MDR1* mRNA	19	35	Yes, $P = 0.03$
[23]	*MDR1* mRNA	43	51	Yes, $P = 0.005$
[25]	MRK16	47	150	Yes, $P < 0.00001$
[26]	MRK16	58	52	Yes, $P = 0.0003$
[27]	MRK16	27	52	No
[28]	JSB_1/C219	53	51	Yes, $P < 0.01$
[29]	$MRK16_{efflux}$	75	171	Yes, $P = 0.0001$
[48]		72	193, elderly	Yes, $P = 0.0001$
[30]	*MDR1*-PCR	Not mentioned	188	No
[31]	MRK16	74	38	Yes, $P = 0.048$
[47]	MRK16	41	69	Yes, $P = 0.0001$

*MRK16, JSB_1, C219, P-glycoprotein specific monoclonal antibodies. *MDR1* mRNA, mRNAse protection or mRNA slot-blot analysis of *MDR1* expression. *MDR1*-PCR, polymerase chain reaction of *MDR1* mRNA.

Table 2. Assays for MDR1 *expression*

Assay	Comment
MDR1 in situ hybridisation	*MDR1* gene not amplified
MDR1-PCR	No quantification
RT–PCR, RNAse protection	Quantification of mRNA
Immunocytochemistry	Few cells needed, cytology possible
	Low sensitivity
MRK16 staining by flow cytometry	Combined analysis with other antigens
	Good sensitivity
Rhodamine retention	Analysis of functional efflux

JSB1, have been used in immunocytochemistry, but this assay has not been widely used because of the difficulty in quantitating the results. For applications in haematology, flow cytometry (FACS) can be used to determine Pgp levels in viable cells by using monoclonal antibodies, such as MRK16, which recognises an extracellular epitope. This technique allows the expression of Pgp to be detected in different subsets of cells. Such studies have demonstrated that *MDR1* is heterogeneously expressed in subsets of normal as well as leukaemic blood cells. High *MDR1* expression levels were observed in CD34+ immature haematopoietic cells as well as in lymphocytes, CD56+ natural killer cells and macrophages [33]. In leukaemic blast cells, Pgp expression is frequently associated with the expression of the CD34 antigen [25]. More recently, coexpression of Pgp and CD34 was demonstrated in AML blast cells [26, 29]. In a recent study by Leith, a disconcordant expression of *MDR1* was observed in $CD34^+$ cells, i.e. Pgp staining and the Rhodamine fluorescent dye retention assay identified AML cases with different properties [29]. This study points to the possibility that *MDR1* expression may vary and/or have multiple functional properties in $CD34^+$ AML cells. These data suggest that the expression of *MDR1* in immature stem cells is conserved during leukaemic transformation [25, 26, 28, 32–34].

In addition to *MDR1*/Pgp expression, the Pgp-mediated efflux of cytostatic agents (daunorubicin, doxorubicin, vincristine) or of the fluorescent probe Rhodamine 123 can be determined in cell suspensions. Using such a functional assay, the effect of Pgp inhibition by a drug resistance-modulating agent can be evaluated [35–37]. Together, these assays may be used to analyse the MDR profile of AML cells obtained from individual patients. Only a few studies have attempted to correlate the expression of *MDR1* with the *in vitro* drug sensitivity [21, 33, 38, 39]. Beyond the considerable technical difficulties of these clonogenic assays, interpretation of the results is hampered by the fact that other mechanisms of drug resistance may also be involved.

Clinical significance of MDR1

Several studies have addressed the clinical value of *MDR1* expression in cancer. The first example of a correlation of *MDR1* expression with relapse of childhood soft tissue carcinoma was reported by Chan and associates [40]. *MDR1* expression seems to be more frequently expressed in several haematological tumours. In pretreated Non-Hodgkin's lymphoma, the reported incidence of P-glycoprotein staining varied from 2 to 49% in untreated patients and 64% in pretreated patients, while with mRNA analysis these figures were 22–50% and 30–60%, respectively [9–16]. As summarised by Yuen and Sikic [16], it is presently unclear whether MDR expression has a significant impact on the response to therapy in lymphomas. Most studies suggest that P-glycoprotein-positive patients may have a poor prognosis as compared to negative patients. A high frequency of P-glycoprotein expression is also observed in relapse multiple myeloma [38, 41–44]. In untreated myeloma, MDR does not seem to have an important impact on the outcome of treatment [45], while in VAD (vincristine, doxorubicin, dexamethasone) refractory myeloma *MDR1* expression is almost invariably observed [41, 44]. In these patients, the frequency and intensity of P-glycoprotein expression is correlated with the prior exposure to doxorubicin and vincristine, respectively [46].

Several studies have reported a prognostic significance of

MDR1 expression in AML specimens obtained from untreated patients. A significantly lower probability of achieving a complete remission was observed in patients with *MDR1* expression as determined by either RNA assays [19, 21–23] or P-glycoprotein staining [25, 26, 28, 29, 47]. No correlation was found in two studies using these assays [27, 30]. The lack of agreement between some studies emphasises the need for standardising the most informative assay(s) for *MDR1* analysis in AML specimens. Even with highly specific assays, it is uncertain to what extent low numbers of *MDR1* expressing cells are relevant for the outcome of clinical treatment. In an attempt to evaluate the relevance of difference numbers of *MDR1*-positive blast cells, Te Boekhorst showed that even the presence of small numbers of these cells (1–5%) represents an increased risk of refractory disease [48]. These data suggest that small numbers of MDR cells are relevant for the response to treatment in *de novo* AML, and that assays should be developed which are capable of detecting *MDR1* expression in such small cell fractions.

In one study, it was found that *MDR1* expression at diagnosis has a negative impact not only on CR rate, but also on remission duration and on survival [22]. More recently Leith and coworkers [48] performed an extensive study in untreated AML patients, in which they demonstrated that elderly patients have a higher frequency of P-glycoprotein expression which is associated with enhanced drug efflux. In these patients, P-glycoprotein expression significantly reduced the probability of achieving a complete remission and also survival was shorter. These data confirm the earlier reports that *MDR1* expression is an independent prognostic variable for response in AML. In acute lymphoblastic leukaemia (ALL), P-glycoprotein is observed in 38% of cases, and in a multivariate analysis it was shown to be an independent, poor prognostic factor for response and survival in both children and adults [50].

Other mechanisms of pleiotropic drug resistance in AML

MRP. Typical MDR has now been recognised as an important cause of *in vitro* resistance to many antileukaemic drugs such as anthracyclines, epipodophyllotoxins and amsacrine. However, in spite of the fact that *MDR1* confers clinical resistance in AML, other mechanisms of resistance also seem to be involved. The *MRP* gene is a member of the superfamily of membrane drug transporters and located on chromosome 16. Like Pgp it confers resistance to anthracyclines. *MRP* expression has been reported in a variety of untreated and refractory haematological malignancies including acute and chronic leukaemias [51–53]. The frequency of *MRP* expression in untreated AML to a level surpassing that of normal blood leucocytes is approximately 50% [51]. The expression in pretreated patients is higher [53]. In cell lines and in AML specimens, coexpression of *MRP* with Pgp has been observed [51, 54, 55]. At present, it remains unclear as to what is the clinical relevance of *MRP* expression in AML. Certainly, there are currently no means of circumventing this protein through reversal agents. Genistein is the single available reversal agent of *MRP*, but it cannot be used in patients. Recently, an Australian group reported that deletion of the *MRP* gene in AML patients with the (46,inv(16)) karyotype was associated with a favourable effect on disease-free survival and overall survival [56].

Recently, a vault transporter protein was identified in doxorubicin-resistant cell lines and designated LRP [57]. Expression has been observed in blast cells of AML patients and seemed increased in patients who responded poorly to anthracyclines [58]. A summary of drug resistance in AML is shown in Table 3.

CLINICAL MODULATION OF MULTIDRUG RESISTANCE

Since the recognition of MDR as an independent mechanism of drug resistance, attempts have been made to downregulate or to circumvent P-glycoprotein using oligonucleotides [59] and protein kinase C inhibitors such as staurosporine, which downregulate *MDR1* expression [60]. Another approach to modulate Pgp is to inhibit its interaction with cytostatic drugs by reversing agents. A direct interaction of Pgp and MDR-reversing agents has been demonstrated with competitive binding experiments using [^{3}H]azidopine or tritiated cytostatic drugs [61]. It is currently accepted that many reversing agents can restore drug accumulation by competing with cytostatic drugs for Pgp-binding sites. These agents include calcium channel blockers, calmodulin inhibitors, immunosuppressive agents, quinolines, indole alkaloids, detergents, steroids and anti-oestrogens [62–69] (Table 4). Several of these reversal agents have common chemical features like a planar aromatic domain and two amino groups, one of which has a cationic charge at physiological pH, and they all are highly lipophilic. Synergistic effects by combining several modulators such as verapamil and cyclosporin or other modifiers have also been described [65]. This observation suggests that the exact mechanism of drug reversal is not identical for all reversing agents. Table 4 shows some examples of these modulating agents and the concentrations required to reverse MDR *in vitro*. *In vitro* reversal of drug resistance has also been investigated in fresh AML specimens. Verapamil, cyclosporins and other reversing agents increase the intracellular retention of daunorubicin in AML blast cells which express the *MDR1* phenotype, but not of drug-sensitive AML cells [26, 31, 39, 54, 70–73]. These agents augment the cytotoxicity of anthracyclines in *in vitro* clonogenic assays [74–78].

Clinical trials have been performed with several MDR modulators. Phase II/III studies in solid tumours have been reported that combined verapamil, quinidine and trifluoroperazine with doxorubicin and epirubicin, respectively, demonstrating that the serum levels achieved were not sufficient to modulate MDR-expressing cells [12, 79–81]. The feasibility of quinine in combination with mitoxantrone and Ara-C was studied in patients with acute leukaemia [82]. Other combinations included verapamil plus vinblastine or etoposide [83], high-dose verapamil plus chemotherapy, diltiazem plus vincristine, tamoxifen and vinblastine and nifedipine plus etoposide [61, 83–85]. These trials have shown that such an approach is feasible, although generally the clinical effect in refractory patients has been limited. However, for optimal modulation of drug resistance, it would be necessary to achieve a steady state or trough plasma concentration, which is one or two times higher than the concentration needed *in vitro* to circumvent MDR. With many of these modulators, the variability of resorption, protein binding and pharmacokinetics lead to unpredictable plasma levels and frequently to unacceptable toxicity. At present, cyclosporin and its analogue SDZ PSC 833 [86] are the most promising compounds for clinical drug modulation, since these agents can be adminis-

Table 3. Relevant pathways of drug resistance in acute myeloid leukaemia

Type of resistance	Drug(s) involved	Mechanism(s)
Ara-C resistance	Cytosine-arabinoside (Ara-C)	Kinetic resistance Deoxycytidine kinase levels activity Rapid deamination dCTP pools (↑)* DNA polymerases activity (↓) DNA repair (↑)
Typical MDR†	Anthracyclines Daunomycin Doxorubicin Mitoxantrone Epipodophyllotoxins Etoposide Vinca alkaloids Vincristine Vinblastine Other Amsacrine Actinomycin-D Pactitaxel Colchicine	*MDR1* overexpression
Atypical MDR	Like typical MDR	Expression of MRP‡ Expression of LRP Decreased/altered activity of Topoisomerase IIα
Other mechanisms	Several drugs such as Anthracyclines Alkylating agents Cisplatin	Glutathione *S*-transferase Glutathione peroxidase Glutathione levels (↑) Metallottionine

*↓ or ↑, decreased or increased. †MDR, multidrug resistance. ‡*MRP*, multidrug resistance-associated protein

Table 4. MDR reversal agents and the in vitro *concentration* required for inhibition of P-glycoprotein*

Calcium channel blockers	Immunosuppressive drugs
Verapamil (6–10 μM)	Cyclosporin A (0.8–2 μM)
Nifedipine (35 μM)	11-Methyl-leucine cyclosporine (1 μM)
Nicardapine (3–10 μM)	SDZ PSC 833 (1 μM)
Niguldipine (10 μM)	SDZ 280-446 (0–1 μM)
Bepridil (4 μM)	FK506 (3 μM)
	Rapamycin (3 μM)
Calmodulin antagonists	Antibiotics
Trifluoperazine (3–5 μM)	Cefoperazone (1000 μM)
Prochlorperazine (4 μM)	Ceftriaxone (1000 μM)
Fluphenazine (3 μM)	Erythtromycin (650 μM)
trans-Flupenthixol (3–5 μM)	Tetracycline (4000 μM)
Vinca alkaloid analogs	Miscellaneous compounds
Vindoline (20–50 μM)	Dipyridamole (5–10 μM)
	Quinidine (10 μM)
	Chloroquine (10–50 μM)
	Yohimbine (5 μM)
	Amiodarone (4 μM)
	Solutol HS 14 (4–14 μM)
	Cremaphor EL
	GF

*Concentrations in parentheses are those shown to have an effect in reversing MDR *in vitro*.

tered so effective serum levels are reached and can be combined with cytotoxic agents without unacceptable toxicity.

If a modulator is added, increased toxicity of the MDR-related anticancer drugs may occur because of inhibition of P-glycoprotein in normal tissues by the modulator. For example, $CD34^+$ normal haemopoietic stem cells are potentially harmed by a combined regimen of a modulator plus myelotoxic drugs, because these cells express Pgp. Therefore, extra myelosuppression may be observed in patients treated with such a combination. More severe myelosuppression in these patients may result from inhibition of P-glycoprotein in CD34 stem cells and their progeny [87]. Moreover, many modulators alter the pharmacokinetics of MDR-related drugs through modulation of Pgp in the biliary canaliculi and the renal tubuli, blocking biliary and renal drug elimination. Such an effect was first observed in mice and in patients treated with verapamil and doxorubicin [88]. The cross-over design in the latter study demonstrated that the peak levels, the elimination half-life and the volume of distribution of doxorubicin were increased by verapamil at a plasma concentration of ±5 μM. Increased toxicity was also observed in clinical studies such as those combining verapamil with VAD [38, 43], bipredil plus vinblastine [89], cyclosporin A plus daunorubicin and high-dose cytarabine [90], cyclosporin A with VAD [91] and cyclosporin A plus etoposide [92]. These studies indicate that Cyclosporin at effective blood levels leads to an approximately two-fold increase of the plasma exposure to etoposide, daunorubicin and doxorubicin. Consequently, in trials

attempting to modulate resistant tumour cells, the dose of these drugs when combined with an MDR modulator should be reduced by 25–50% in order to avoid dose-intensification.

The first case report of clinical reversal of drug resistance in haematology was published in 1988. A VAD-refractory myeloma patient was treated with VAD plus verapamil and a response was observed [93]. In a larger group of patients with multiple myeloma or non-Hodgkin's lymphoma, high-dose verapamil was infused in order to achieve effective plasma concentrations of verapamil [12, 42]. The high plasma concentrations of verapamil required for Pgp inhibition induced cardiac arrhythmias in the majority of patients. In a phase I/II study of verapamil combined with VAD in a group of 22 patients cardiac monitoring was needed and most patients had EKG irregularities. It should be noted, however, that approximately half the patients achieved a response [38].

In order to avoid these cardiovascular side-effects, an NCI phase I trial was performed in patients with refractory lymphoma or sarcoma [94], which demonstrated the feasibility of achieving effective and safe plasma concentrations of dexverapamil and nordexverapamil. In a subsequent cross-over trial of dexverapamil combined with EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone), several responses were noted in 64 analysed patients [95]. Notably, half the *MDR1*-positive patients responded as compared with 1/8 patients with no or weak expression. In these extensively treated patients, other acquired or intrinsic factors of drug resistance may have played a role.

The feasibility of cyclosporin as an MDR reversal agent, combined with VAD, was evaluated in 21 myeloma patients with advanced disease, who had progressed after or on VAD [91]. In this heavily pretreated group of patients, 58% of patients with *MDR1*-positive plasma cells responded as compared with 33% of *MDR1*-negative patients. The steady state serum cyclosporin concentration achieved with continuous infusion of 7.5 mg/kg/day in these patients was suboptimal at 1000–1100 ng/ml. The toxicity was mild which may be due to the fact that the pharmacokinetics of doxorubicin were not significantly different from historical controls. More recently, we have performed a co-operative trial with Dr J. P. Marie in 22 myeloma patients who were refractory to primary treatment with alkylating agents or VAD, using oral SDZ PSC 833 combined with VAD by continuous infusion. In this dose-escalating schedule of SDZ PSC 833 given twice daily, peak plasma levels were ±2500 ng/ml and trough levels were >1000 ng/ml at the highest dose level of 15 mg/kg/day. A 2-fold increase of the plasma area under the curve (AUC) of doxorubicin and of the hydroxyl metabolite was observed in the majority of the patients. For this reason, the dose of the cytotoxic agents had to be reduced. The dose-limiting toxicities were intestinal neuropathy and marrow hypoplasia, which seemed to be associated with increased organ exposure to vincristine and doxorubicin, respectively. Interestingly, a number of clinical responses were noted, which were associated with a proportional reduction of plasma cells expressing the MDR phenotype (Sonneveld and colleagues, manuscript submitted).

This study will be followed by phase II studies in Europe and the U.S.A. in VAD-refractory patients, in order to explore the potential benefit of SDZ PSC 833 in truly refractory myeloma. The definitive proof of the validity of MDR reversal should come from randomised studies in patients who fail conventional therapy. Two such studies have been performed in multiple myeloma. Dalton and associates investigated the effect of verapamil added to VAD in a phase III trial. No effect was observed using verapamil at a suboptimal dose [96]. In an ongoing co-operative study of the EORTC and HOVON study groups, the effect of cyclosporin on myeloma refractory to alkylating agents is being evaluated. These and other studies are performed with standard dosages of VAD in the presence of the reversal agent. Such an approach may make it impossible to determine whether P-glycoprotein modulation in the tumour cells is responsible for the observed effect. Treatment with cyclosporin A or SDZ PSC 833 leads to reduced biliary clearance of most P-glycoprotein-transported drugs and thereby to an increased plasma AUC of these cytotoxic agents. In fact, standard chemotherapy schedules, where doses are not reduced, combined with a reversal agent at effective dosages represents a condition of dose escalation. Therefore, future comparative trials with MDR modulators have to take into account the fact that the doses of VAD and other P-glycoprotein-transported drugs have to be reduced in order to evaluate properly the role of MDR reversal.

In AML, some clinical experience with reversal of multidrug-resistance has been obtained. In 1990, a refractory AML patient was treated with daunorubicin/Ara-C to which cyclosporin A was added, resulting in a short remission [37]. More recently, 20 refractory or relapsed patients were treated with mitoxantrone/etoposide, to which cyclosporin was added. Although several responses were noted, the toxicity of this regimen was considerable and seemed to be related to severe marrow hypoplasia [97]. There was a high incidence of life-threatening infections, which may be related to prolonged neutropenia. In another study, quinine was used as a reversing agent in refractory AML, and it was well tolerated [82].

The largest study to date was performed by List and colleagues [90] when 42 patients with refractory and/or relapse AML or blast-crisis CML were treated with daunorubicin plus high-dose cytarabine to which cyclosporin-A was added in a dose-escalation design. The toxicity of cyclosporin was dose-dependent and included prolongation of myelosuppression, nausea and hyperbilirubinaemia. The plasma levels of daunorubicin were elevated in patients who received a high dose of cyclosporin-A. In this patient group, 62% achieved a complete remission. The results of this study indicate that it is possible to combine a drug-reversal agent such as cyclosporin with combination chemotherapy in AML patients without unacceptable toxicity.

In AML, there are several ongoing studies with the promising reversal agent SDZ PSC 833. One such study is being conducted by the Southwest Oncology Group, which combines high-dose Ara-C with an anthracyclin and SDZ PSC 833. In addition, several studies in primary refractory or early relapse patients have been initiated. An important question in these studies is whether the reversal agent should be used in patients with refractory disease only, or in patients with tumours expressing the MDR phenotype. In elderly AML patients, a high incidence of P-glycoprotein expression is observed, and it is associated with a poor probability of achieving a complete response or a long lasting remission [48]. Therefore, studies with MDR reversal agents are warranted in this patient group during initial treatment.

At present, several studies have been initiated to investigate the clinical effect of MDR modulation in a cross-over or randomised phase III design. A summary of ongoing randomised studies in AML is presented in Tables 5 and 6.

Table 5. Randomised trials of Pgp modulation in poor risk acute leukaemia

Institution/investigator	Dates	Modulator	Diagnoses	No. of patients	Chemotherapy
GOELAM MAQ2 Solary	1992–1995	Quinidine (30 mg/kg/i.v.)	Acute leukaemia	315	ID-AraC+Mitoxantrone
SWOG 9126 List	1993–?	CsA (16 mg/kg/i.v.)	AML	220	HiDAra-C+DNR
French MultiCentre Study Assouline	1994–?	Dexverapamil (250 mg q4H p.o.)	ALL	100	HiDAra-C+VAD
HOVON Daenen+Sonneveld	1995–?	CsA (12.5 mg/kg/i.v.)	AML (<65y,RoR)	80	Mitoxantrone+VP16
MRC Burnett	1994–?	CsA (2.5–5 mg/kg/i.v.)	AML (<60, RoR)	>100	DNR+AraC+6TG

q, every; p.o., oral.

Table 6. Randomised trials with PSC 833 in AML

Institution/investigator	Date	Dosage*	Diagnosis	Chemotherapy
ECOG/Greenberg	1995	10 mg/kg	Refractory-AML	Mitoxantrone+VP16 (MEC)+AraC
CALGB/Schiffer	1995	10 mg/kg	AML >60 years	DNR+VP16+AraC
HOVON, MRC/SAKK	1995	10–20 mg/kg	AML >60 years	DNR+AraC

*Continuous i.v. daily.

CONCLUSION

Multidrug resistance represents a form of pleiotropic drug resistance that has a prognostic value in untreated AML and in refractory multiple myeloma, and possibly in non-Hodgkin's lymphoma. It may affect the outcome of current chemotherapy protocols. Therefore, *MDR1* expression should be systematically investigated in prospective studies. In addition, reversal of drug resistance may be attempted by adding drug resistance modifying agents such as cyclosporins to standard chemotherapy. The clinical value of such an approach has to be established in randomised phase III studies.

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