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# Clinical importance of P-glycoprotein-related resistance in leukemia and myelodysplastic syndromes – first experience with their reversal

**Summary** P-gylcoprotein (P-gp) expression in mononuclear bone marrow cells was analyzed in 119 patients, including 60 with chronic myelogenous leukemia (CML), 48 with myelodysplastic syndromes (MDS), and 11 with acute myelogenous leukemia (AML). For P-gp measurement an immunocytological method using monoclonal antibodies C219, 4E3, and MRK 16 and the reverse transcription-polymerase chain reaction technique were applied. According to our results obtained in healthy volunteers using the immunocytological method, the limit for P-gp overexpression was set at ≥10% P-gp-positive mononuclear *bone marrow cells* and at ≥30% P-gp-positive mononuclear *peripheral blood cells*. All 42 CML patients in chronic phase had normal P-gp expression. P-gp overexpression was demonstrated in four of six patients in accelerated myelogenous blast cell phase and in four of 12 CML-BC patients. Of eight CML patients in blast crisis (BC) with normal P-gp expression, partial remission was achieved in three and minor response in five after prednisone/vindesine therapy. All four of the 12 CML-BC patients with P-gp overexpression did not respond to this therapy. Normal P-gp expression was seen in 41 (85.4%) of 48 untreated MDS patients. While P-gp overexpression did not develop during therapy in any of the myelodysplastic syndrome patients treated with low-dose ara-C alone, four of eight treated with low-dose ara-C plus GM-CSF and four of 11 treated with low-dose ara-C and IL-3 developed P-gp overexpression after therapy. Furthermore, 11 AML patients at primary diagnosis, including five AML patients with P-gp overexpression, who were treated with idarubicin, vepesid, and cytarabine V (ara-C) showed a complete remission. Additionally, one daunorubicin-cytarabine-pretreated refractory AML patient was treated with the oral form of the P-gp modulator drug dexniguldipine and achieved complete remission for a duration of 7 months. Our results suggest that in CML patients in BC, P-gp expression influences outcome after therapy. Further more, studies in a larger series of patients are necessary to prove the efficacy and toxicity of idarubicin/vepesid and cytardbine – or dexniguldipine-containing – therapy in relation to P-gp expression of AML patients.

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## Introduction

Since the identification of a transmembrane glycoprotein known as 170-kD P-glycoprotein (P-gp) and coded by the multidrug-resistance (mdr)1 gene, the field of resistance research has focused on intensive in vitro and ex vivo characterization of the pattern of P-gp-related resistance [7]. It is assumed that P-gp actively pumps P-gp-related substances (such as anthracyclines, vinca alkaloids, podophyllotoxins, paclitaxel, and actinomycin D) out of the cell in an ATP-dependent manner [6]. Some reports have recently been published on P-gp expression in patients with chronic myelogenous leukemia (CML) in chronic phase or blast crisis (BC) [3, 12, 19] or with myelodysplastic syndromes (MDS) [10, 13]. However, few data are available regarding P-gp expression during therapy. This analysis is aimed at examining the influence of P-gp expression on treatment outcome in CML patients with BC and in patients with acute myelogenous leukemia (AML) who were treated with idarubicin, vepesid, and ara-C. Additionally, P-gp expression after the last-mentioned therapy and after treatment of MDS patients will be discussed. Many in vitro reports and phase-I trials have been published on P-gp-reversing substances, so-called modulators [15]. We report here on our first experience with a new modulator named dexniguldipine in a refractory AML pa-

tient. Dexniguldipine is an enantioselective pure (99.5%) (R)-enantiomer of the dihydropyridine derivative niguldipine and has P-gp-modulating potency [9].

## Materials and methods

In this study P-gp expression was examined in bone marrow-mononucleated cells of 42 CML patients in chronic phase, six CML patients in accelerated phase, 12 CML patients in BC, 48 patients with MDS, and 11 AML patients. Patients' age ranged from 21 to 63 years.

### Treatment protocols

Eleven AML patients in primary diagnosis were treated by protocol of the EORTC (European Organization for Research on Treatment of Cancer) Leukemia Cooperative Group. This AML-10 (study coordinators: R. Zittoun, F. Mandelli, NC. Gorin) protocol prescribes idarubicin 12 mg (later 10 mg)/$m^2$, on days 1, 3, 5; vepesid 200 mg/$m^2$, days 1–5; Ara-C 25 mg/$m^2$ as i.v. bolus, followed immediately by 100 mg/$m^2$ given as a continuous daily infusion for 10 days.

The CML-BC patients were treated with prednisolone (75 mg for 1 week, then 50 mg in the second week and 25 mg/third week p.o.) and vindesine (2 mg/$m^2$ i.v. per day on 2 days per week for 3 weeks).

MDS patients were treated according to a randomized EORTC protocol (study coordinators: H. Gerhartz, H. Zwierzina) applying six cycles of:
Arm A: low-dose Ara-C $2\times10$ mg/$m^2$ s.c./day on days 1–14, break for seven days.
Arm B: low-dose Ara-C $2\times10$ mg/$m^2$ (days 1–14) plus GM-CSF $1\times150$ μg s.c./day (days 8–21).
Arm C: low-dose Ara-C $2\times10$ mg/$m^2$ (days 1–14) plus IL-3 $1\times150$ μg s.c./day (days 8–21).

### Evaluation criteria

Criteria for complete remission (CR), partial remission (PR), no change (NC), or progressive disease (PD) were estimated using UICC and WHO criteria. Minor response (CMR) was defined as a 50% reduction in blast cells and/or blood transfusion.

The accellerated phase in CML patients was defined as a stage between about 20 and 30% blasts and promyelocytes in peripheral blood, combined with an aggravation of the patient's condition.

Blast crisis is defined as more than 30% blasts and promyelocytes in peripheral blood or more than 50% blasts and promyelocytes in bone marrow.

### Monoclonal antibodies

MoAb C219 (Centocor, Malvern, USA) is a mouse monoclonal antibody ($IgG_{2a}$ class) directed toward an intracellular epitope of the human mdr1-encoded P-gp [11]. However, MoAb C219 also recognizes the mdr2-encoded glycoprotein, and reaction with myosin or contamination of some charges of purified MoAb C219 with an anti-A blood group antibody has been published [4, 5, 16].

MoAb 4E3 is a mouse monoclonal antibody directed toward an extracellular epitope of the human mdr1-encoded P-gp. This MoAb is also an $IgG_{2a}$-class antibody [1]. MoAb 4E3 was originally a gift of Dr. Arceci (Dana-Faber Institute, Boston, MA, USA) and was later ordered from Signet Laboratories, Inc., Dedham, MA, USA. MoAb 4E3 specifically recognizes the human mdr1 P-gp but not the mdr2 product.

MoAb MRK 16 (Behring, Vienna, Austria) is a mouse monoclonal antibody ($IgG_{2a}$) directed toward an extracellular epitope of the human mdr1-encoded P-gp. This MoAb specifically recognizes the human mdr1 P-gp, but it, too, does not recognize the mdr2 product [8].

### Cell lines

For standardization we used a human T-lymphoblastic leukemia cell line (CCRF-CEM) with low P-gp expression and its variants ($CCRF\text{-}CEM_{ACT400}$, $CCRF\text{-}CEM_{VCR1000}$; gift of Dr. V. Gekeler, Byk Gulden, Constance, Germany). "ACT 400" or "VCR1000" means actinomycin D (MSD, Sharp Dohme) at a concentration of 400 ng/ml, or vincristine (Lilly, Germany GmbH) at a concentration of 1000 ng/ml, as needed to maintain maximal P-gp expression in these cell lines. Using MoAbs C219 and 4E3, P-gp expression in mononuclear cells of bone marrow (BM) was determined as described by Nüssler [14]. Using MoAb MRK16, P-gp expression was determined with the indirect immunocytological method. For MRK16 estimation, the mononuclear cells in BM were concentrated and washed using the method for MoAb C219. Pellets were resuspended in PBS + 0.05% $NaN_3$ + 20% FCS at a final concentration of $5\times10^6$ cells/ml. After 15 min on ice, 200 μl cell suspension was incubated with 10 μl MoAb MRK16. In a separate tube 10 μl of the negative control (donkey anti-mouse MoAb IgG (H+L); Jackson Immuno Research Laboratories, Inc., West Baltimore, USA) was added to 200 μl cell suspension. Both tubes were incubated on ice for 30–60 min. Samples were centrifuged and washed (see MoAb C219). Pellets were resuspended in 200 μl PBS + 0.05% $NaN_3$ + 2% FCS and 5 μl of the B-PE-conjugated secondary antibody (donkey anti-mouse IgG (H+L), Jackson Immuno Research Labs, Inc., West Baltimore, USA) added. Then both tubes were incubated on ice in darkness for 30–45 min. After the cells had been washed once, they resuspended in PBS + 0.05% $NaN_3$ + 2% FCS for flow cytometric analysis. Bone marrow specimens were taken before and after therapy when the leukocyte count was at least 1.5 g/l. The P-gp level was measured within 24 h.

To confirm our data on the mRNA level, RNA extraction, reverse transcription, and PCR amplification were performed in vitro according to standard protocols. Total cellular RNA was isolated using the cesium chloride-isothiocyanate method. Equal amounts of RNA from each source were reverse transcribed using Moloney murine leukemia virus transcriptase and oligo dt primer. The synthetic oligonucleotide primers used for the amplification of P-glycoprotein were MD 41 (5′ AGGCTTGCTG-TAATTACCC 3′) and MD 42 (5′ TATGGTACCTG-CAAACTCTG 3′). The PCR conditons were 94° C for 1 min 65° C for 1 min, and 72° C for 2 min. It was run for 30 cycles; 10 μl PCR product was electrophoresed in a 1.5% agarose gel and stained with ethidiumbromide [20].

### Statistics

The U test was used for comparison of patients' P-gp values and response rates (CSS software). $P$ values $<0.05$ were considered statistically significant.

## Results

### Comparison of MoAbs C219, 4E3, and MRK16 in vitro and ex vivo

As mentioned in Materials and Methods, MoAb C219 alone is cross-reactive to the mdr2-coded glycoprotein. Therefore, MoAbs MRK16 and 4E3 were used in cell lines and patients. First, P-gp expression was conducted in $CCRF\text{-}CEM_{ACT400}$ and $CCRF\text{-}CEM_{VCR1000}$ cell lines

**Table 1** Comparison of MoAbs C219, MRK16, and 4E3 and the PCR technique in vitro

| Cell line | MoAb C219 P-gp-positive cells (%) | MoAb MRK16 P-gp-positive cells (%) | MoAb 4E3 P-gp-positive cells (%) | PCR technique |
|---|---|---|---|---|
| CCRF-CEM/ACT 400 | 85 | 25 | 98 | — |
| CCRF-CEM/ACT 400 | 92 | 30 | 98 | — |
| CCRF-CEM/ACT 400 | 90 | 15 | 100 | positive |
| CCRF-CEM/VCR 1000 | 88 | 12 | 100 | — |
| CCRF-CEM/VCR 1000 | 95 | 53 | 96 | — |
| CCRF-CEM/VCR 1000 | 90 | 28 | 100 | positive |

using MoAbs C219, MRK16, and 4E3 and the PCR technique (Table 1). The two cell lines mentioned with a high P-gp overexpression showed a difference between MoAbs C219 and 4E3 as well as with the PCR technique. Compared with these result, the MoAb MRK16 detected P-gp expression only at a low level. Furthermore, 22 AML patients and 13 ALL patients were examined with MoAbs C219, MRK16, and 4E3 (Table 2). When compared with the data for MoAbs C219, 4E3 the MRK16 results corresponded in only 23 (65.7%) of the patients examined (Table 2, marked"*"). These in vitro and ex vivo results were the reason for not using MoAb MRK16 in further routine examinations.

Because in 22 healthy persons P-gp expression of mononucleated BM cells was between 0 and 8% when MoAbs C219 and 4E3 were used the limit for P-gp overexpression was defined as $\geq 10\%$ P-gp-positive cells in BM. In the peripheral mononucleated blood cells of 15 healthy persons, however, the range of P-gp expression was between 11 and 25% P-gp-positive cells when MoAbs C219 and 4E3 were used. This is why the limit for P-gp overexpression in the peripheral mononucleated blood cells was determined at $\geq 30\%$.

**Table 2** Comparison of MoAbs C219, MRK16, and 4E3 in AML and All patients

| Patient no. | Diagnosis | MoAb C219 P-gp-positive cells in BM (%) | MoAb MRK16 P-gp-positive cells in BM (%) | MoAb 4E3 P-gp-positive cells in BM (%) |
|---|---|---|---|---|
| 1* | AML/first diagnosis | 0 | 4 | 0 |
| 2 | AML/first diagnosis | 16 | 4 | 25 |
| 3* | AML/first diagnosis | 0 | 1 | 0 |
| 4* | AML/first diagnosis | 3 | 0 | 0 |
| 5 | AML/relapse | 78 | 3 | 82 |
| 6 | AML/relapse | 49 | 5 | 63 |
| 7* | AML/first diagnosis | 0 | 0 | 0 |
| 8 | AML/first diagnosis | 0 | 18 | 0 |
| 9* | AML/first diagnosis | 2 | 0 | 0 |
| 10* | AML/first diagnosis | 0 | 5 | 0 |
| 11 | AML/relapse | 18 | 6 | 26 |
| 12 | AML/first diagnosis | 0 | 22 | 0 |
| 13* | AML/first diagnosis | 0 | 0 | 0 |
| 14 | AML/first diagnosis | 0 | 16 | 0 |
| 15* | AML/first diagnosis | 0 | 0 | 0 |
| 16 | AML/relapse | 32 | 0 | 38 |
| 17 | AML/relapse | 27 | 0 | 42 |
| 18 | AML/first diagnosis | 0 | 15 | 0 |
| 19* | AML/first diagnosis | 0 | 0 | 0 |
| 20* | AML/first diagnosis | 0 | 0 | 0 |
| 21* | AML/first diagnosis | 0 | 35 | 0 |
| 22* | AML/first diagnosis | 0 | 0 | 0 |
| 23* | T-ALL/first diagnosis | 0 | 0 | 0 |
| 24* | B-ALL/first diagnosis | 0 | 0 | 0 |
| 25* | T-ALL/first diagnosis | 0 | 0 | 0 |
| 26* | T-ALL/first diagnosis | 0 | 0 | 0 |
| 27* | T-ALL/first diagnosis | 0 | 0 | 0 |
| 28* | C-ALL/relapse | 0 | 0 | 0 |
| 29* | C-ALL/relapse | 4 | 6 | 0 |
| 30* | C-ALL/relapse | 5 | 2 | 0 |
| 31* | B-ALL/first diagnosis | 0 | 0 | 0 |
| 32 | T-ALL/first diagnosis | 25 | 0 | 28 |
| 33 | C-ALL/relapse | 25 | 0 | 23 |
| 34* | C-ALL/relapse | 5 | 0 | 5 |
| 35* | C-ALL/relapse | 4 | 0 | 0 |

### P-gp expression in CML, MDS, and AML patients

All 42 CML patients examined in chronic phase had normal P-gp expression. P-gp overexpression was demonstrated in four of six patients in myeloid accelerated phase and in four of 12 CML-BC patients. Three of these four CML-BC patients had a myeloid BC, one a lymphatic. These four CML-BC patients had 30, 35, 85, and 91% blasts in peripheral blood. In these patients' peripheral blood a P-gp overexpression with a range between 35 and 92% P-gp-positive cells was measured using MoAbs C219 and 4E3.

Forthy-eight patients were examined in the MDS group. Normal P-gp expression was seen in 41 (85.4%) of 48 MDS patients: ten refractory anemia (RA), one refractory anemia with ring sideroblasts (RAS), 25 refractory anemia with blast excess (RAEB), and five refractory anemia with blast excess in transformation (RAEB-t). P-gp overexpression was found in seven (14.6%) of 48 untreated MDS patients; three were classified RAEB-t and four RAEB.

### Follow-up of P-gp expression during treatment

No induction and/or selection of P-gp overexpression during BC therapy was observed in CML patients. Four MDS (two RAEB- and two RAEB-t) patients were treated with low-dose Ara-C alone. In none of these four patients was P-gp overexpression observed during therapy; three (two RAEB- and one RAEB-t) of them had PR, one RAEB-t patient NC in response to therapy.

In four (two patients with RAEB-t, two with RAEB) of eight MDS patients treated with Ara-C and GM-CSF, P-gp overexpression was estimated after treatment (at least two cycles). The RAEB-t patients had PD and the RAEB patients NC.

In another four of the 11 MDS patients treated with Ara-C and IL-3, P-gp overexpression was demonstrated after at least two cycles. All four RAEB patients also showed no response to treatment; i.e., three patients had NC and one PD.

Six of 11 AML patients with normal P-gp expression before therapy were treated with the ICE protocol. Only one of these showed P-gp overexpression combined with PR after the first cycle of the ICE protocol. In this case the patient was reinduced with the same protocol, and CR without P-gp overexpression was achieved.

### P-gp expression in relation to response

Four of 12 (33%) patients with CML-BC (four myeloid BC, one lymphatic BC) showed P-gp overexpression with NC to prednisone/vindesine. Compared with these results, five CML-BC patients with normal P-gp expression demonstrated MR (two lymphatic BC, three myeloid BC) and three CML-BC patients with normal P-gp expression (Myeloid BC) PR.

In MDS patients investigation of the relation between response and P-gp expression seems not to be useful because they were not treated with P-gp-related drugs.

Five of 11 AML patients at primary diagnosis who were treated according to the ICE protocol demonstrated P-gp overexpression before treatment. All five patients achieved CR, as did the other six patients with normal P-gp expression before therapy.

### First result of an AML patient with P-gp overexpression following treatment with the oral form of dexniguldipine

Acute myelogenolus leukemia (FAB M2) was diagnosed in a female patient (60 years) in November 1992: in BM aspiration 85% blasts, in peripheral blood leukocyte count 38.5 G/l, hemoglobin 10.6, platelet count 18.0 G/l. In addition, P-gp overexpression (58% P-gp-positive cells in BM) was displayed.

The patient was treated with daunorubicin (30 mg/$m^2$, days 1–3), and Ara-C (200 mg/$m^2$, days 1–7). NC was observed after this therapy. Duration of leukopenia (leukocyte count $<1.5$ G/l) was 32 days. For 8 days fever ($>38.5$ C) and for 3 days diarrhea was observed. The leukocyte nadir was 0.3 G/l. Six weeks after the first induction course the same therapy was administered again and dexniguldipine at a dose of 2500 mg/d p.o. (3-3-4 tablets) was given, days 1–9, plus daunorubicin 30 mg/$m^2$, days 4–6, and Ara-C (200 mg/$m^2$, days 4–10). Before beginning treatment the blast count in BM was 37%, P-gp expression in BM was 64%, and in peripheral blood the leukocytes were 2.1 G/l, hemoglobin 10.1, and platelets 11.0 G/l. Leukopenia (leukocyte count $<1.5$ G/l) lasted 35 days. The nadir was also 0.3 G/l. Duration of fever ($>38.5$ C) was 7 days.

As possible side effects of dexniguldipine, a subileus was observed from day 10 to 15, and mild dizziness for 1 h at a blood pressure of 120/60 on day 11 after therapy was documented. On day 38 (after commencement of therapy) histological examination demonstrated a normal blast count in BM; leukocytes were 1.6 G/l, Hb 11.3, platelets 155 G/l. For technical reasons, no aspiration was performed; the patient refused a repeat of this diagnostic examination. CR was documented for 7 months, and then the patient relapsed again.

## Discussion

P-gp expression in monoculceated BM cells in leukemia patients is an important resistance marker, because we now have the possibility to use cytostatic drugs not related to P-gp resistance or to use so-called P-gp modulators to reverse P-gp-related resistance. This last point remains to be proven in phase-II and -III studies.

The consequence of comparing MoAbs C219, MRK16, and 4E3 is to avoid MRK16 for routine determination of P-gp. MoAb 4E3, for instance, can replace MoAb MRK16. The prevalence of P-gp overexpression before therapy in CML and MDS patients corresponds with the published results [3, 10, 12, 13, 19].

For CML-BC patients with P-gp overexpression, a prednisone/vindesine therapy was not seen to be efficient in our study. Although a small group of patients with P-gp overexpression were treated, this therapy should be replaced with drugs that are only minimally or not at all related to P-gp transport.

Although it has been stated that P-gp overexpression is not a relevant marker in MDS patients [10], two aspects of this analysis are remarkable. First, it should be noted that P-gp overexpression was seen only in RAEB and RAEB-t patients. Second, it is surprising that during therapy P-gp overexpression was observed with low-dose Ara-C and IL-3 or GM-CSF, but not with low-dose Ara-C alone. In conclusion, it can be assumed that P-gp overexpression in MDS patients is related to the FAB classification and that in further studies the phenomenon of P-gp expression during low-dose Ara-C and IL-3 or GM-CSF therapy should be controlled. At this time there are no indications that IL-3 or GM-CSF induced and/or selects P-gp overexpression [17]. The speculative assertion that GM-CSF or IL-3 might directly influence P-gp expression in MDS patients must be proven in large clinical trials and in vitro.

Preliminary results regarding the response rates of ICE in relation to P-gp overexpression underscore the findings made in vitro by other authors [2] and by ourselves in refractory leukemia patients [14] that idarubicin can overcome P-gp-related resistance. Additionally, this analysis shows that also idarubicin, vepesid and Ara-C as not strong by P-gp-related drugs induce and/or select P-gp overexpression after treatment. Treatment with so-called modulators of P-gp may possibly be an efficient new therapy concept for refractory or relapsed leukemia patients. One of these modulators is dexniguldipine. Dexniguldipine shows binding activity to P-gp, but inhibition of PKC resulting in an antiproliferative effect was also demonstrated [18]. In contrast to the modulation effect, however, long-term administration of dexniguldipine may be necessary for antiproliferative potency. Treatment of a refractory AML patient with the oral form of dexniguldipine was successful and toxicity tolerable. At the moment, the effectiveness of the i.v. form of dexniguldipine in AML patients remains to be proven in a large clinical trial.

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