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CD56 and PGP expression in acute myeloid leukemia: impact on clinical outcome

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Background and Objectives. Overexpression of P-glycoprotein (PGP), a multidrug-related (MDR) protein, is one of the most important factors responsible for reduced drug sensitivity in acute myeloid leukemia (AML). Recently, we demonstrated that the presence of CD56 antigen, an isoform of the neural adhesion molecule, in AML cells is a negative independent prognostic factor for the achievement of complete remission (CR) and correlates with shorter survival. Since in our previous report we observed a more frequent PGP expression in $CD56^+$ patients, we hypothesized that the reduced response to chemotherapy in this group of patients was due to increased PGP-mediated drug efflux. To confirm this hypothesis in this study PGP and CD56 expression on AML cells was correlated with other clinical and biological features and treatment response.

Design and Methods. Immunophenotypic analysis, including evaluation of CD56 and PGP expression, was performed using multiparameter flow cytometry on fresh and/or cryopreserved blast cells, obtained after informed consent, from bone marrow and/or peripheral blood of 143 consecutive newly diagnosed AML cases at the time of diagnosis. Samples expressing CD56 in at least 15% or more cells were considered as positive ($CD56^+$). PGP expression was expressed as a mean fluorescence index (MFI) i.e. as the ratio of sample mean fluorescence channel and the isotypic control mean fluorescence channel.

Results. Overall results showed that 67/143 cases were $PGP^-/CD56^-$, 23/143 were $PGP^+/CD56^+$, 40/143 were PGP^+/CD56- and the remaining 13/143 were $PGP^-/CD56^+$. $CD56^+$ and PGP^+ on AML cells significantly reduced the CR rate (83% in the $PGP^-/CD56^-$ group vs 60% in the PGP-/$CD56^+$ group, 46% in the $PGP^+/CD56^-$ group and 58% in the $PGP^+/CD56^+$ group, $p = 0.002$). In addition we observed a significantly higher proportion of total failures in patients expressing PGP or CD56 compared to in the group not expressing either (73% vs 27%, respectively; $p = 0.0001$). CD56 and PGP overexpression influenced the overall survival: in fact, the median survival of $CD56^+$ and PGP^+ patients ranged from 10 to 23 months, while the actuarial survival of $CD56^-/PGP^-$ patients at 5 years is 52% ($p = 0.023$).

Interpretation and Conclusions. Our data underline the independent negative prognostic role of PGP and CD56 expression in acute myeloid leukemia. Since the mechanism by which CD56 reduces drug sensitivity is still unknown, further investigations are required.

Key words: AML, PGP, CD56, MDR, complete remission.

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Resistance to chemotherapy is a major obstacle to the cure of acute myeloid leukemia (AML). Leukemic cells may exhibit resistance as a consequence of their inherited genotype, alternatively they may become resistant under selection of sub-lethal exposure to anticancer drugs, as frequently occurs in the clinical management of leukemia. Inherited or acquired genomic alterations lead to the synthesis of gene products responsible for reduced drug sensitivity.[1-2] Among these, P-glycoprotein (PGP) overexpression has been demonstrated to correlate with poor prognosis. PGP is a 170 kDa transmembrane protein encoded by the MDR-1 gene located in the humans on the long arm of chromosome 7, and is physiologically expressed in most normal tissues.[3-5] In leukemic cells high levels of PGP result in a reduction of intracellular drug concentrations[2,6] and several studies published recently have clearly documented a negative influence of PGP overexpression on the outcome of AML patients.[7-9] In addition, more recently, it has been demonstrated that in AML

patients the presence of CD56 antigen, an isoform of the neural adhesion molecule, on leukemic blasts, is an independent adverse prognostic factor for the achievement and duration of complete remission, also in good risk patients.[10-16] Since in our previous report[14] we observed more frequent PGP expression in CD56$^+$ patients, we hypothesized that the reduced response to chemotherapy in this group of patients was due to increased PGP-mediated drug efflux.

With the aim of confirming this hypothesis and thus identifying a cohort of patients who could benefit from more intensive treatment, in this study PGP and CD56 expression on blast cells of 143 consecutive newly diagnosed AML patients were correlated with other clinical and biological features and treatment response.

Design and Methods

One hundred and forty-three consecutive, adult AML patients diagnosed between January 1995 and December 2000 at the Division of Hematology of Udine (83 cases) and of Siena (60 cases) entered the study. The diagnosis was based on FAB criteria.[17] Patients with acute promyelocytic leukemia cases were excluded from the study because they are addressed to different treatment. One hundred and thirty-three patients were treated according to the ongoing protocol of the Institutions. The first course of this protocol consisted of a 7-day continuous infusion of cytosine-arabinoside (200 mg/m^2) and idarubicin (12 mg/m^2, in 1 hour) for 3 days. Post-induction therapy included the administration of high dose cytosine-arabinoside (3000 mg/m^2, twice daily, days 1-6) and a further course with mitoxantrone (10 mg/m^2 i.v. days 1-4), etoposide (80 mg/m^2 i.v. days 1-4), and cytosine-arabinoside (1000 mg/m^2 i.v. days 1-4) (MEC). Patients > 65 years old received lower doses of the drugs. The protocol allowed for allogeneic or autologous stem cell transplantation whenever possible. Response to treatment was classified as follows: death during induction (DDI, death during or after the first or second course of therapy with aplastic or hypocellular bone marrow); complete remission (CR, cellular marrow with less than 5% of blast cells, a neutrophil count ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L and no evidence of leukemia in other sites); primary resistance (cellular marrow with > 5% blast cells or evidence of leukemia in other sites); early relapse (relapse within 6 months after achieving remission). Primary resistance and early relapse accounted for the total early failures.

CD56 and PGP expression

CD56 was assessed by flow cytometry (FACScalibur, Becton Dickinson, San José, CA, USA) using an anti-CD56 phycoerythrin (PE)-conjugated MoAb (Leu 19, NCAM 16.2, Becton Dickinson) on fresh and/or cryopreserved blast cells, obtained after informed consent, from bone marrow and/or peripheral blood at the time of diagnosis. Normal lymphocytes were excluded from the analysis by using two-color staining, coupling CD56 and CD13, CD33 or CD34 antibodies after gating leukemic cells on forward and side light scatter parameters. Samples expressing CD56 in at least 15% of cells were considered as positive (CD56$^+$).[14] PGP expression was evaluated by an indirect immuno-fluorescence technique using the MRK-16 antibody (Kamya, Biochemicls, Seattle, WA, USA) as previously described.[9] Results were expressed as a mean fluorescence index (MFI) i.e. as the ratio of sample mean fluorescence channel and the isotypic control mean fluorescence channel. Cases with MFI ≥ 6 (i.e. with MFI exceeding the higher values found on normal blood cells and on non-MDR cell lines), were considered as overexpressing PGP (PGP$^+$). In all cases 10,000 events were acquired and analyses were performed by the CellQuest software (Becton Dickinson).

Cytogenetic analysis

Cytogenetic analysis was performed with a G-banding technique with Wright's stain on bone marrow aspirates obtained at the time of diagnosis. We examined metaphase cells from short-term cultures and at least 20 cells were analyzed. Chromosomal abnormalities are described according to the *International System for Human Cytogenetic Nomenclature* (*ISCN, 1995*).[18] The t(8;21), inv(16) and t(16;16) were defined as favorable prognostic abnormalities; abnormalities of 7/7q-, 5/5q-, del(11)(q23), del(3), t(9;22), and more than 3 chromosomal abnormalities (complex karytotypes) were defined as unfavorable. Other karyotypic abnormalities or a normal diploid karyotype were defined as indicating intermediate prognosis.

Statistics analysis

Two-sided Yates corrected χ^2 test and Fisher's exact test were employed to compare differences between groups. Multivariate and univariate logistic regression analyses were used to identify variables affecting response to therapy. All marginally significant parameters in univariate analysis were included in multivariate analysis. Then a backward procedure was adopted to remove the least significant factors until only variables with significant

Table 1. Clinical and biological characteristics of patients according to PGP and CD56 expression on blast cells.

	PGP⁻/CD56⁻	*PGP⁺/CD56⁻*	*PGP⁻/CD56⁺*	*PGP⁺/CD56⁺*
WBC × 10^9/L	48±66 23 (0.2-329)	47±46 29 (0.8-152)	41±58 18 (0.2-181)	39±38 27 (1-150)
Age	49±15 51 (14-80)	43±16 46 (16-70)	48±17 50 (16-68)	50±19 56 (15-80)
CD34⁺	45/67 (67%)	20/40 (50%)	10/13 (77%)	12/22 (55%)
Karyotype				
Unfavorable	13/53 (25%)	11/33 (34%)	4/10 (40%)	9/20 (45%)
Favorable	40/53 (75%)	21/33 (66%)	6/10 (60%)	11/20 (55%)

Table 2. Response to therapy in AML patients according to CD56 and PGP expression on blast cells.

	Total	*Complete remission§*	*Primary resistance*	*Early relapse**	*Total failures°*
PGP⁻/CD56⁻	67	49/59 83%	10/59	6/49 12%	16/59 27%
PGP⁺/CD56⁻	40	18/39 46%	21/39	9/18 50%	30/39 77%
PGP⁻/CD56⁺	13	6/10 60%	4/10	3/6 50%	7/10 70%
PGP⁺/CD56⁺	23	11/19 58%	8/19	5/11 45%	13/19 68%

§PGP⁻/CD56⁻ vs PGP⁺/CD56⁻ and PGP⁻/CD56⁺ and PGP⁺/CD56⁺; p = 0.002;
**PGP⁻/CD56⁻ vs PGP⁺/CD56⁻ and PGP⁻/CD56⁺ and PGP⁺/CD56⁺; p = 0.00006;*
°PGP⁻/CD56⁻ vs PGP⁺/CD56⁻ and PGP⁻/CD56⁺ and PGP⁺/CD56⁺, p = 0.0001;
Total failures: primary resistance + early relapse.

value were retained. Disease-free survival and overall survival were calculated by the Kaplan-Meier method. Differences among groups were compared by log-rank test.

Results

One hundred and forty-three consecutive AML patients at diagnosis were evaluated for PGP and CD56 expression. Sixty-eight were males and 75 females with a median age of 52 years (range 15-81). According to FAB criteria, 4 patients were classified as having M0, 32 as M1, 36 as M2, 38 as M4, 31 as M5, 1 as M6 and 1 as M7.

Immunophenotypic pattern showed that CD56 antigen was expressed in 35/143 (24%) cases, and PGP was overexpressed in 63/143 (44%). Sixty-seven out of 143 (47%) were PGP and CD56 negative (PGP⁻/CD56⁻), 13/143 (9%) expressed only CD56, 40/143 (28%) expressed only PGP, whilst PGP and CD56 co-expression (PGP⁺/CD56⁺) was observed in 23/143 (16%) cases. In addition, a significantly higher level of PGP was documented in CD56⁺ patients than in CD56⁻ cases (MFI = 10±2.6 vs. 8±2.1, $p = 0.01$). The clinical and biological characteristics of patients according to PGP and CD56 staining are shown in Table 1. Age, white cell count and CD34 positivity were comparable among groups. As previously reported, a higher frequency of unfavorable karyotypic abnormalities was found in patients expressing at least one of the two proteins, without significant differences among the three groups compared to in PGP⁻/CD56⁻patients.

Response to therapy

Response to therapy was evaluable only in 127/143 patients who entered the study, since 10 patients did not receive any therapy because of refusal, advanced age or concomitant diseases and 6 patients (2 in the PGP⁻/CD56⁻ group, 1 in the PGP⁺/CD56⁻ group, 2 in the PGP⁻/CD56⁺ group and 1 in the PGP⁺/CD56⁺ group) died during induction therapy. Eighty-four out of the 127 (66%) achieved CR and 44/127(35%) showed primary resistance. Moreover, 23/84 (27%) patients who obtained CR, relapsed within 6 months and were considered *early failures*. Treatment response according to PGP and CD56 expression was also analyzed and 4 groups of patients were identified: PGP⁺/CD56⁺, PGP⁺/CD56⁻, PGP⁻/CD56⁺ and CD56⁻/PGP⁻. The CR rate was significantly lower in patients expressing CD56 antigen or PGP protein or both compared to in CD56⁻/PGP⁻ patients. In fact, as shown in Table 2, CR was achieved in 11/19 (58%) PGP⁺/CD56⁺cases, in 18/39 (46%) PGP⁺/CD56⁻, in 6/10 (60%) PGP⁻/CD56⁺ but in 49/59 (83%) PGP⁻/CD56⁻, $p = 0.002$. DDI were equally distributed among the groups and were excluded from the analysis. Early relapses were observed more frequently in those patients expressing PGP or CD56 than in negative patients (17/35, 49% vs 6/49 12%, $p = 0.0006$), without any difference between the 3 positive groups. Finally, there were significantly more total failures in patients expressing PGP or CD56 than in PGP⁻/CD56⁻ patients (50/68, 74% vs 16/59, 27%, $p = 0.0001$) (Table 2). In univariate analysis white blood cell count at onset ($p = 0.03$) and unfavorable chromosomal abnormalities ($p = 0.05$) were also associated with treatment failure. All parameters maintained statistical significance in multivariate analysis (Table 3).

CR duration and survival

The median duration of CR in PGP⁻/CD56⁻

Table 3. Factors affecting response to therapy: multivariate analysis.

	Odds ratio	*CI**	*p*
WBC (> 30,000/μL)°	1.01	1.00 - 1.21	0.03
CD56 (> 10%)°	1.83	0.86 -2.38	0.05
PGP (MRK-16 MFI >6)	0.16	0.05 - 0.47	0.0009
Karyotype	0.41	0.17 - 1.02	0.02

**CI = confidence iunterval. °Cut-off.*

patients was 12 months, while in PGP$^+$/CD56$^+$, PGP$^-$/CD56$^+$and PGP$^+$/CD56$^-$ patients it was 6, 6 and 5 months, respectively (Figure 1a). Finally, survival analysis was performed and, as shown in Figure 1b, in patients expressing PGP or CD56 or both, the survival ranged from 10 to 23 months, while in CD56$^-$/PGP$^-$ patients the actuarial survival at 5 years is 52% (p = 0.023).

Discussion

Failure of leukemia treatment may depend on several factors not always well understood. Among these, it is well known that overexpression of PGP is able to reduce intracellular *in vitro* drug concentrations leading to resistance to many chemotherapeutic agents widely employed in clinical protocols.[20-23] However, other clinical and biological features have been associated with a reduced capacity to achieve and/or maintain CR, such as age, number of blasts, cytogenetics or CD34 expression.[27,28] More recently, a negative role in the treatment outcome of AML patients has been attributed to the presence on the leukemic cells of CD56 antigen.[29-31] In fact, some previous reports suggest that the presence of CD56 antigen on myeloid blast cells identifies subgroups of patients with an unfavorable outcome. Baer *et al.*[10] described significantly shorter CR duration (8.7 months vs not reached, p = 0.01) and significantly shorter overall survival (OS) (16.5 months vs not reached, p = 0.008) in CD56$^+$ t(8;21) adult M2 blast cells, suggesting a strong prognostic value of CD56 expression in this AML subtype. Murray *et al.*[12] and Ferrara *et al.*[13] reported the same prognostic value only in APL patients, but they did not confirm its prognostic value in multivariate analysis. Di Bona *et al.*[15] failed to demonstrate the influence of CD56 positivity on CR duration and OS in the whole group of AML analyzed (171 cases), but they found a significantly higher relapse rate in the CD56$^+$ APL subgroup (32 cases), suggesting a different weight of CD56 expression in the AML FAB subtypes. In contrast, in our previous paper,[14] analyzing 152 consecutive non-APL AML patients we reported a lower probability of achieving CR and shorter survival irrespective of FAB subtype, and Ciolli *et al.*[15] found better event-free survival in CD56 negative patients. The mechanism by which CD56 influences response to therapy is yet unknown. Previously reports showed that normal CD56$^+$ cells express high levels of PGP[32,33] and that inhibition of PGP efflux function using either specific monoclonal antibodies or pharmacological inhibitors, or a decreased of PGP expression using antisense oligonucleotides resulted in a reduction of NK and CD8 cytolytic activity.[34] In addition it was recently demonstrated that the mutant

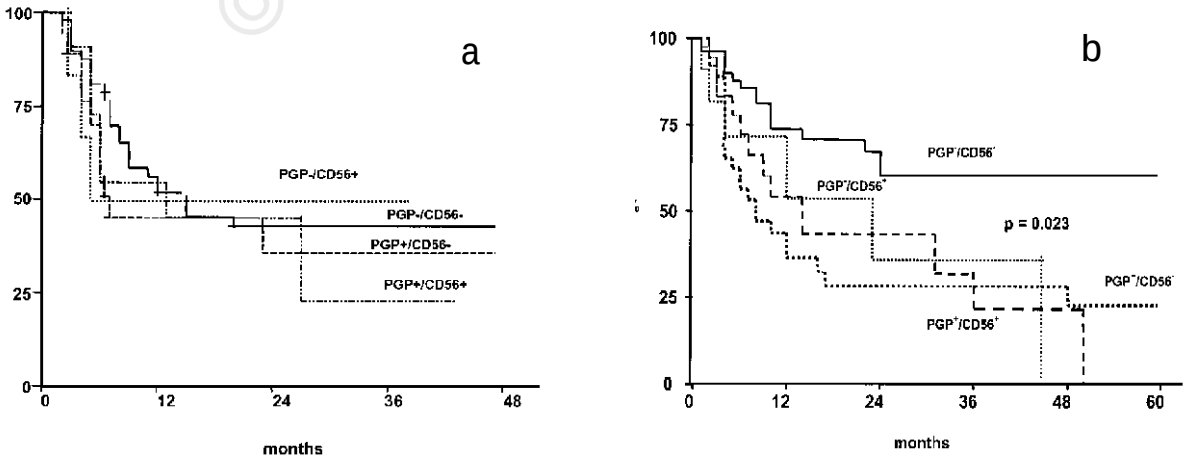

Figure 1. Disease-free survival (a) and overall survival (b) curves of AML patients according to CD56 and PGP expression.

MDR3435T allele is associated with reduced PGP activity in CD56+ natural killer cells.[35] Based on the observation that also CD56+ leukemic cells frequently co-express PGP, we hypothesized[14] that the reduced responsiveness to chemotherapy in CD56+ AML patients could be due to the efflux pump activity of PGP. In the present study we have investigated the incidence of CD56 and PGP co-expression on AML blast cells and their impact on clinical outcome. CD56 antigen was present in 35/143 of our patients (24%), without any significant correlation with other biological or clinical features, except PGP. Clinical outcome was significantly worse in patients expressing at least one protein: only 18/39 PGP+ (46%), 6/10 (60%) CD56+ and 11/19 (58%) PGP+/CD56+ patients achieved complete remission, compared to 49/59 (83%) negative patients, $p = 0.02$. The difference considering failures is even more marked: 20/29 (69%) in CD56+ cases, and 43/58 (74%) PGP+ cases ($p = 0.00006$) compared to 27% in PGP–/CD56– patients. The association of CD56 and PGP did not further worsen prognosis: in fact a comparable number of early failures was observed. The role of CD56 antigen as an adverse prognostic factor was also confirmed by the survival analysis: in our series of cases the median duration of overall survival was significantly shorter in patients CD56+ and/or PGP+ compared to in PGP–/CD56– patients (8, 10, 10 months vs 36 months, respectively) ($p = 0.023$) (Figure 1b).

In conclusion, our data highlight the independent negative prognostic role of PGP and CD56 expression in acute myeloid leukemia. The mechanism by which CD56 contributes to reduced drug sensitivity remains to be investigated: an association with other known or unknown transport cellular proteins, able to divert anticancer drugs to their cellular target, can be hypothesized.

Contributions and Acknowledgments

DR, DD and MM were responsible for the study design, analysis of results and manuscript preparation. RS, SG and AG were responsible for clinical management. AG performed cytogenetic analyses and contributed to a critical analysis of the paper. PM and AM performed immunophenotypic analyses. RF and FL supervised the study and critically revised the final version of the paper. DR and DD were primarily responsible for the publication. DR and DD were responsible for all tables and figures.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

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What is already known on this topic

Previous studies have shown that both reactivity for CD56 and expression of MDR1/PGP on acute myeloblastic leukemia (AML) blast cells correlate with a poor disease outcome.

What this study adds

In the present study it is shown that both blast cell features - CD56 and PGP expression - are independent factors for predicting response to therapy in AML, a $CD56^-/PGP^-$ phenotype also being associated with a significantly better overall survival.

Potential implications for clinical practice

Although confirmatory investigations are needed, this study points to the potential utility of analyzing both CD56 and PGP expression in AML at diagnosis for predicting response to therapy.

Alberto Orfao, Associate Editor (Salamanca, Spain)