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Prognostic significance of CD56 antigen expression in acute myeloid leukemia

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Background and Objectives. CD56 antigen expression has been reported in several hematologic malignancies. In acute myeloid leukemia (AML)M2 with t(8;21) and acute promyelocytic leukemia (APL) it has been found to be consistently associated with an unfavorable prognosis, whereas in other AML subtypes its role remains uncertain. We investigated CD56 expression in a cohort of AML patients in order to assess its frequency and prognostic relevance.

Design and Methods. Immunophenotypic analysis including that of CD56 antigen was available for 171 consecutive AML patients (139 with AML and 32 with APL), enrolled between December 1995 and December 1999 at a single institution. A sample of fresh bone marrow cells taken at diagnosis was recorded as positive when at least 20% of the cells double-stained with specific monoclonal antibodies against CD56 and CD33 antigens.

Results. CD56 positivity was demonstrated in 37 cases (21.6%). Its frequency was lower in M4 (6%) and higher in M5 (37%). The median percentage for $CD56^+$ blasts was 56% (range 21-99%). CD56 positivity did not correlate with age, sex, blast count, favorable or unfavorable cytogenetics at diagnosis, nor did it influence the outcome in terms of complete remission (CR) duration (606 vs. 417 days, p=n.s.) or overall survival (OS) (210 vs. 277 days, p= n.s.). In the APL subgroup a significant difference in relapse rate was found at 3 years (71.4% in the CD56 positive group vs. 12% in the CD56 negative group, p=0.005).

Interpretation and Conclusions. Our data confirm that CD56 positivity in APL patients at diagnosis is associated with a worse prognosis, suggesting that close molecular monitoring is necessary in CD56 positive APL patients. In contrast, the prognostic role of CD56 remains uncertain in the other AML subtypes.

Key words: CD56 antigen, acute myeloid leukemia, acute promyelocytic leukemia, all-trans retinoic acid.

CD56 antigen, a member of the immunoglobulin supergene family, is an isoform of the well-characterized neural cell adhesion molecule (NCAM) that mediates cell-to-cell interaction[1,2] and is possibly involved in cell-mediated cytotoxicity. This antigen, usually expressed on most normal natural-killer (NK) cells, is also found in a subset of $CD3^+$ cytotoxic T-cells and a small population of $CD4^+$ T-cells and monocytes[2] and has been detected on various hematopoietic neoplasms, including clinically aggressive lymphomas and myeloma.[3,4] Interestingly, a recently described myeloid/NK cell acute leukemia, with morphologic features similar to those of APL, expresses this molecule.[5]

Limited evidence suggested that CD56 positivity could be associated with extramedullary leukemic infiltration[6] but, in a large series, it was not found to correlate with karyotype, immunophenotype or extramedullary leukemic infiltration.[7]

Several recent studies showing a potentially prognostic role of CD56 have renewed interest in this molecule. In particular, an unfavorable outcome has been associated with CD56 positivity and $HLA\text{-}DR^-$, $CD33^+$, $CD16^-$ myeloid/natural killer acute leukemia,[5] in FAB M2 subtype AML with t(8;21)[8] and in acute promyelocytic leukemia (APL).[9,10] However, more evidence is required to assess the prognostic role of CD56 positivity in other AML subtypes, especially considering the highly heterogeneous treatment schedules reported in different studies. Recently, Raspadori *et al.* retrospectively

evaluated clinical outcome according to CD56 positivity in 120 AML non-APL patients after a standard 3+7 chemotherapy.[11] They found a significant reduction in CR rate and a shorter survival in the CD56$^+$ group and a strong correlation with unfavorable karyotype and P-glycoprotein (Pgp) overexpression. On the other hand, Ciolli *et al.* in their retrospective analysis of 125 AML patients, did not found any significant correlation between CD56 expression and biological parameters at diagnosis and clinical outcome, but they showed a shorter event-free survival in the 23 CD56$^+$ patients.[12]

In this study, we investigated the expression of CD56 with regards to age (< or > 60 years) and APL diagnosis in a cohort of AML patients treated in a single institution with specific protocols in order to assess the positivity rate of CD56 antigen, its expression and prognostic value.

Design and Methods

From December 1995 to December 1999, 228 patients were diagnosed as having AML (39 with APL) at our Institution. One hundred and seventy-one consecutive untreated patients with AML (32 with APL) for whom a complete immunophenotypic study was available were included in this study. The diagnosis of AML was unequivocal according to morphologic, cytochemical, and immunophenotypic criteria. The diagnosis of APL was confirmed by cytogenetic or molecular analysis. Patients were grouped according to FAB criteria.

One hundred and thirty-seven received intensive chemotherapy. Thirty-two APL patients were treated with the AIDA protocol[13] based on all-trans retinoic acid (ATRA) and idarubicin, irrespective of their age. Patients with AML younger than 60 years (54 cases) were treated with idarubicin 10 mg/m^2 dd 1-3, cytosine arabinoside 200 mg/m^2 dd 1-7, and etoposide 100 mg/m^2 dd 1-5 (ICE protocol). Those aged 60 or older (51 cases) were treated with oral idarubicin 15 mg/m^2 dd 1,3,5; oral etoposide 100 mg/m^2 bid dd 1,3,5; and thioguanine 100 mg/m^2 bid dd 1-5 (ETI protocol), in the framework of a collaborative study involving 22 centers of Internal Medicine of the Veneto Region (Network Ematologico Veneto, NEVE group).[14]

Immunophenotypic analysis

Immunophenotypic analysis was performed on whole fresh bone marrow samples taken at diagnosis. A panel of FITC and PE-conjugated monoclonal antibodies was used. This panel included anti-CD3 (UCHT1, Beckman-Coulter (BC), Miami, FL, USA or SK7 Becton Dickinson Biosciences (BDB), San José, CA, USA) CD4 (Caltag, Burlingame, CA, USA), CD7 (8H8.1, BC), CD8 (SK1, BDB), CD10 (HI10a, BD or J5, BC), CD13 (SJ1D1, BC), CD14 (RM052, BC), CD15 (80H5, BC), CD16 (3G8, Caltag), CD19 (SJ25-C1, Caltag), CD33 (WM-54, Dako, Golstrup, DK), CD34 (8G12, BD), CD45 (2D1, BD), CD56 (NCAM16.2, BD), CD57 (HNK-1, BD), CD61 (SZ21, BC), CD64 (10.1, Caltag), CD117 (NU c kit, Caltag), CD235a – glycophorin A (CLB-AME-1, Caltag), HLA-DR (TU36, Caltag), MPO (CLB-MPO-1/1, BC), and TdT (a mixture of HT1$^+$HT4$^+$HT8$^+$HT9, BC). One-, two- or three-color flow cytometry was performed on FACScalibur (BDB) cytometers. Fluorescence signals were collected using four-decade logarithmic amplification. A specific antigen was considered positive when > 20% of blast cells were stained above the negative control. Accordingly, a case was recorded as CD56$^+$ when, in a double-staining procedure with anti-CD33, more than 20% resulted CD56 positive.

Cytogenetic analysis

Cytogenetic analysis was performed on bone marrow cells from unstimulated cultures after 24 hours of incubation in Chang medium (Irvine Scientific, Santa Ana, CA, USA). Chromosomes were characterized by the trypsin G-banding method;[15] karyotypes were described according to the ISCN nomenclature[16] by analysis of at least 25 metaphases. When the number of metaphases obtained was too low for G-banding analysis, fluorescent *in situ* hybridization (FISH) was performed on interphase-cells. Commercial probes (ONCOR, Gaithersburg, MD, USA) were used. The preparation of probes, hybridization, washing conditions and signal detection were performed according to manufacturer's instructions. Karyotypes were defined as favorable, intermediate or unfavorable according to MRC criteria.[17]

Molecular analysis

Polymerase chain reaction (PCR) amplification of PML/RARα was performed in all cases of an established or suspected diagnosis of APL, as previously reported.[18]

Statistical analysis

Spearman's rank correlation test was used to analyze qualitative parameters and CD56 positivity; a Mann-Whitney test was used for quantitative parameters and CD56 positivity. Survival analysis was performed using the Kaplan-Meier method. Cox models were used for multivariate time dependent analyses and logistic regression for analyses of categorical variables. Age, gender, absolute number of blast cells, cytogenetic risk group, CD56 antigen positivity, and kind of therapy were considered in

Table 1. Clinical data in 171 AML patients according to CD56 antigen expression at diagnosis.

	CD56 expression	
	Negative Median (range)	*Positive Median (range)*
Age (years)	61 (17-87)	65 (17-86)
Sex (M/F)	76/58	17/20
Platelets (×10⁹/L)	49 (7-532)	78 (12-352)
Blood blasts (×10⁹/L)	2.9 (0-245)	4.5 (0-147)
Secondary AML (y/n)	31/103	10/27
Favorable karyotype	26 (79%)	7 (21%)
Intermediate karyotype	70 (79%)	19 (21%)
Unfavorable karyotype	32 (74%)	11 (26%)

Table 2. Distribution of CD56 antigen positivity according to FAB classification.

	CD56 expression		
FAB	*Negative (%)*	*Positive (%)*	*Total (%)*
0	5 (100)	–	5 (3)
1	43 (81)	10 (19)	53 (31)
2	25 (76)	8 (24)	33 (19)
3	25 (78)	7 (22)	32 (19)
4	15 (94)	1 (6)	16 (9)
5	17 (63)	10 (37)	27 (16)
6	4 (100)	–	4 (2)
7	–	1 (100)	1 (0.6)
Total	134 (78)	37 (22)	171 (100)

univariate and multivariate analyses as prognostic factors influencing DFS and OS. CD56 expression was evaluated not only as a dichotomic variable, but also considering increasing levels of percentage of positivity, namely 21-40, 41-60, 61-80, and 81-100%.

Results

Table 1 summarizes the main clinical data at diagnosis. No difference was found between sex, age, blast cell count, cytogenetic group and CD56 positivity.

Thirty-seven patients (21.6%) showed CD56 expression in 20% blasts or more and were considered CD56 positive, 125 (73%) expressed antigen on 10% or fewer blast cells and 9 patients (7%) expressed it on between 10 to 19% of blast cells. Among CD56⁺ patients, the median percentage of CD56⁺ blast cells was 56% (range 21-99). Six (16%) patients had 21 to 40% CD56⁺ blasts, 13 (35%) 41 to 60%, and 9 (24%) 61 to 80%, 9 (24%) 81% or more. Table 2 shows the distribution in AML subtypes according to FAB classification. There was a similar prevalence in M1, M2, and M3 (19%, 24%, and 22%, respectively); the positivity was lower in M4 (6%) and higher in M5 (37%). The CD56 cellular expression was associated with myeloid CD33 (p=0.02) and monocytic CD14 antigen (p <0.001), but did not correlate with lymphoid markers and CD34 positivity.

An abnormal karyotype was found in 60% of patients at diagnosis. Forty-three patients (26%) had an unfavorable karyotype, 89 an intermediate one (51%) and 35 a favorable karyotype (21%); 31 cases of t(15;17), 2 of t(8;21) and 2 of inv(16) were included in the last group. In 4 cases (2.3%) cytogenetic information was not available. There was no difference in CD56 positivity in the three cytogenetic risk categories (21 to 26%, p=n.s.) (Table 1). One case with APL showed t(11;17), PLZF/RARα rearrangement and CD56 positivity.

With regard to APL patients, 6 had low risk, 18 intermediate and 7 high-risk according to Sanz *et al.*[19] CD56⁺ cases were equally distributed.

One hundred and thirty-seven patients were intensively treated according to age for those with AML (105 patients) and with a specific chemotherapeutic schedule for those with APL (32 patients) (Table 3). Overall 88 patients (64%) obtained CR, 21 (70%) in the CD56 positive and 67 (63%) in the CD56⁻ group. Table 3 shows the clinical results in the three different treatment groups. As expected there was a lower CR rate, mainly due to primarily resistant cases (38% vs. 20%, χ^2 test, p = 0.01), and a shorter CR duration in the older group (χ^2 test,

Table 3. Clinical and laboratory characteristics at diagnosis according to treatment.

	ICE (54 patients)	*ETI (51 patients)*	*AIDA (32 patients)*
Age (years)	46 (17-60)	66 (60-76)	43 (17-83)
Sex (M/F)	25/30	34/17	16/15
Platelets (×10⁹/L)	49 (9-532)	82 (11-514)	23 (7-248)
Blood blasts (×10⁹/L)	4 (0-245)	2 (0-174)	0.7 (0-48)
CD56 positivity (%)	10 (18)	13 (25)	7 (23)
CR (%)	39 (71)[12]	21 (41)*°	27 (87)°
Median survival (dd)	277 (8-1415)	136 (10-1120)	759 (1-1652)
Median DFS (dd)	384 (45-1394)	207 (71-1101)	887 (331-1576)

*χ^2= 0.02; °χ^2= <0.0001.

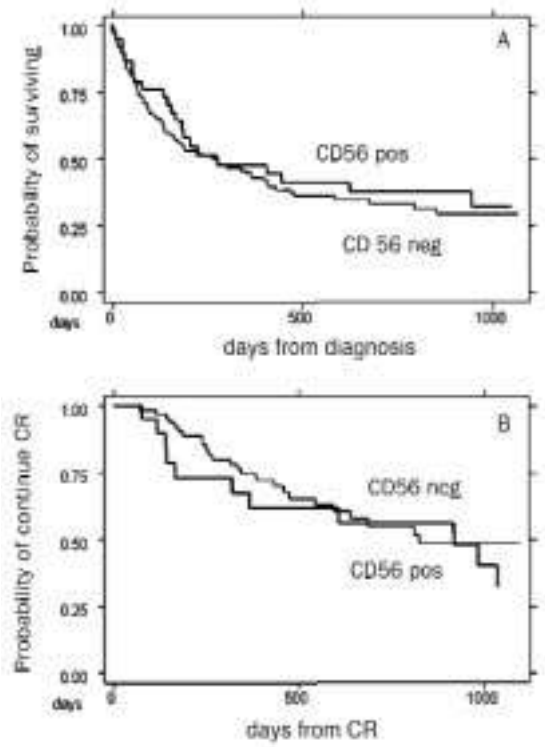

Figure 1. Overall survival (A) and complete remission duration (B) in 171 patients with AML according to CD56 antigen expression.

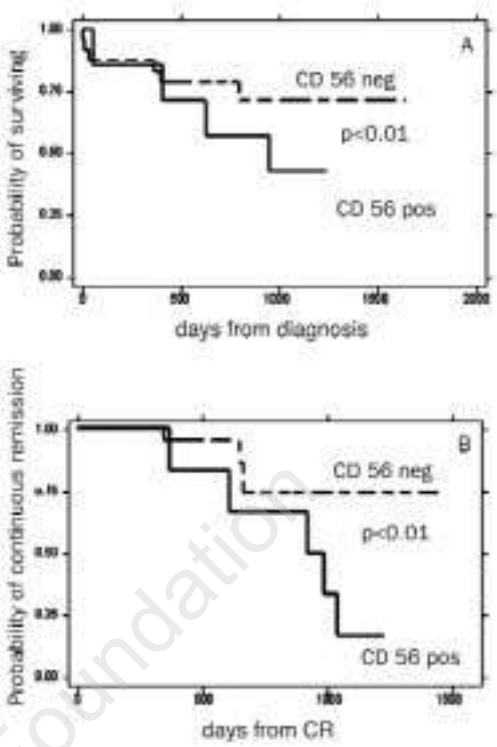

Figure 2. Overall survival (A) and complete remission duration (B) in 32 patients with APL according to CD56 antigen expression.

p<0.0001). This difference was not confirmed in multivariate analysis. Moreover, female patients had a higher probability of reaching CR than males (70% vs. 46%, p = 0.01) in the non-APL group. Unfavorable or intermediate karyotype influenced the probability of obtaining CR in the non-APL group (Odd's ratio 5.8 and 2.4, respectively, p<0.001) but did not influence DFS or OS. CD56 positivity did not influence CR duration or OS (Figure 1A-B). When analyzed separately, CD56 positivity did not influence survival analysis in the ICE and ETI groups or in the intermediate-unfavorable cytogenetic group, but in the AIDA group the median CR duration and OS were significantly shorter in the CD56 positive cases (log rank p<0.01 and p<0.01, respectively) (Figures 2A-B). The number of cases was too low to compare non-APL cases with favorable cytogenetics. When analyzed as a stratified variable, there was trend towards a negative correlation between the percentage of $CD56^+$ cells and CR duration both in APL and in AML, but only in APL was this statistically significant (p=0.03).

Discussion

In this retrospective study, the expression of CD56 antigen was analyzed in 171 consecutive patients with AML. Of them, 105 non-APL AML were homogeneously treated according to age and 32 with APL received specific chemotherapy. In all APL patients the diagnosis had been confirmed by molecular PML/RARα or PLZF/RARα rearrangement. We found that CD56 positivity in AML was a quite common feature, being present in 22% of cases. These data are consistent with those reported by other studies[7,11,12,20,21] in which 16 to 24% of AML cases showed CD56 positivity. Furthermore the higher prevalence of expression of this antigen in M5 FAB subtype was also confirmed.

CD56 positivity has been variously correlated with a worse prognosis probably with results critically depending on cut-off used, number of cases analyzed, age of patients, and clinical pathology considered (i.e. lymphoma, myeloma, AML, acute lymphoblastic leukemia). Our results clearly show that CD56 positivity did not correlate with age, blast count or karyotype at diagnosis and did not influence the outcome in terms of CR. Notwithstanding the limited number of CD56$^+$ cases, only in the APL subgroup was a significant difference in relapse rate demonstrated (71.4% vs. 12% at 3 years, logistic regression estimates Odds ratio = 12.5, 95% CI 1.7-88.7, p=0.012), whereas no differences were shown analyzing both the whole group and the young and elderly groups of AML patients. We also investigated whether the number of CD56 positive leukemic cells could influence prognosis. A higher percentage of CD56$^+$ cells was associated with a negative trend in OS and DFS both in AML and APL. However, statistical significance was not reached in AML.

As regards AML, at variance with our results, Raspadori *et al.*[11] reported that 37 of 152 non-APL AML patients, rated as CD56$^+$ (cut-off set at 15% of leukemic cells), had a lower probability of achieving CR and a shorter survival. Moreover, they found a strong correlation with unfavorable karyotype and Pgp over expression. Legrand *et al.*[23] found a significant correlation between CD56 positivity and unfavorable karyotype, but they were not able to show any correlation with CR rate or survival analysis. Moreover, data reported by Ciolli *et al.*[12] showed a lack of any association between CD56 positivity and karyotype, other parameters at diagnosis or CR rate, but they found a better event-free survival in CD56 negative patients. In our study, we were not able to demonstrate any prognostic value of CD56 antigen positivity in AML patients but, as reported elsewhere, intermediate/unfavorable karyotype influenced CR rate and age was a major factor in worsening CR rate, DFS and OS. These discrepant results could be attributed to the two different regimens (ICE <60 and ETI>60 years) used. However, the significant difference in univariate analysis between the two schedules (Table 3) was not confirmed in multivariate analysis when age was considered together. Moreover, neutrophil recovery period and blood derivative use during induction in patients treated with the ETI protocol lead us to believe that elderly patients were not undertreated.

In summary, a consistent prognostic value of CD56 expression has been confirmed by several authors in two distinct AML subgroups: FAB M2 AML with t(8;21)[8,18] and APL.[9,10] Baer *et al.*[8] clearly documented a shorter CR duration (8.7 vs. not reached, p=0.01) and OS (16.5 mo vs. not reached, p=0.008) in CD56 positive t(8;21) adult AML cases. In our consecutive cohort of adult AML patients 19% had M2 morphology, but only in 2 of 33 was t(8;21) demonstrated. Thus, as in other consecutive series[7] and at variance with pediatric[22] and selected patients,[8] we can not draw conclusions on the t(8;21) M2 AML CD56 positive cases.

As regards APL, Murray *et al.*,[9] reviewing data from the literature, reported a lower CR rate (50% vs. 84%, p=0.025) and OS duration (5 vs. 232 weeks, p=0.019) in CD56$^+$ patients. Ferrara *et al.*[10] reported 100 APL patients homogeneously treated with ATRA plus chemotherapy (AIDA regimen) among whom 15% of the cases showing CD56 positivity had a shorter median DFS (22 mo vs. not reached, p=0.004) and a lower 3-year probability of surviving (73% vs. 86%, p=0.009). The authors outlined the lack of a significant effect on the CR rate and the independent prognostic value of CD56 positivity in multivariate analysis (p=0.04). Our results in 32 APL patients are in partial accordance with the reported data. No difference was observed in CR rate, but a significant difference in relapse rate was found (71.4% vs. 12%, p=0.005), influencing CR duration (log rank, p<0.01) and OS (p<0.01).

These results lead us to hypothesize that well-established negative prognostic factors, such as karyotype, age, and multidrug resistance, abolish the prognostic value of CD56. In contrast, in APL and in M2 associated with t(8;21), in which a higher CR rate and longer DFS are consistently reported, CD56 positivity was able to identify a small group of patients with a worse prognosis. It is intriguing that in APL an increasing percentage of CD56 positive leukemic cells correlated with a worse prognosis. However, we believe that despite the statistical significance, our results need further confirmation because of the low number of cases.

As far as concerns the mechanism underlying the negative prognostic value in CD56$^+$ cases, it is noteworthy that a common feature in the previous series and in the present one is the higher relapse rate. Because of its involvement in the interaction between cells, CD56 could affect cell homing and leukemic extramedullary dissemination.[24,25] However, in our series, no clinical correlation was found with extramedullary localization at diagnosis or at relapse.

In conclusion, CD56 antigen positivity is a distinct adverse factor in the outcome of APL. This

strong evidence, if confirmed by prospective studies, could justify close molecular monitoring and intensification of post-remission therapy in CD56+ APL patients. On the other hand, the prognostic role of CD56 in AML not associated with t(8;21), remains uncertain.

Physicians and centers referring patients

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Contributions and Acknowledgments

EDB was responsible for data and analysis of results and wrote the manuscript. RZ designed in vitro experiments. RS was involved in data management and analysis. NG carried out cytogenetic and molecular analyses and DM was reponsible for cytometric analyses. FR critically examined the data and manuscript. All the authors revised the final version of the paper.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Alberto Orfao, who acted as an Associate Editor. The final decisin to accept this paper for publication was taken jointly by Dr. Orfao and the Editors. Manuscript received August 27, 2001; accepted January 3, 2002.

What is already known on this topic

Expression of CD56 has been found in acute myeloblastic leukemia (AML) at variable frequencies among the different FAB subtypes. Recent studies have shown a correlation between CD56 and a worse prognosis in specific AML subtypes such as acute promyelocytic leukemia and cases with t(8;21)+, although such results remain controversial.

What this study adds

This paper confirms and extends previous observations on the incidence of CD56 within the different AML subtypes: high among M5 cases, intermediate in M1 , M2 and M3 and low among M0, M6 and M4 patients. In addition, it is shown that among acute promyelocytic leukemia, CD56 expression is associated with a poor clinical outcome while within other AML patients it does not show an association with prognosis.

Potential implications for clinical practice

The use of CD56 as a prognostic factor in AML should be restricted to APL where close monitoring of CD56+ cases is suggested.

Alberto Orfao, Associate Editor