

# Expression of CD56 is an unfavorable prognostic factor for acute promyelocytic leukemia with higher initial white blood cell counts

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## Key words

Acute promyelocytic leukemia, all-trans retinoic acid, CD56 expression, chemotherapy, prognostic factor

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The clinical introduction of ATRA has dramatically improved the outcome of APL.<sup>(1–6)</sup> However, 13–33% of patients with APL still relapse after the first remission.<sup>(6)</sup> Therefore, various prognostic factors predicting outcome are being continuously analyzed, and initial high WBC count, low platelet count, and older age have been recognized as significant factors.<sup>(3,5–8)</sup> Recently, several investigators have suggested that the expression of CD56 antigen, a neural adhesion factor, is associated with higher incidence of relapse and poorer outcome in APL.<sup>(9–12)</sup> However, the number of reported cases and follow-up periods are still limited, and there has been no recommendation so far to modify standard treatment of APL on the basis of CD56 expression.<sup>(13,14)</sup> We analyzed the long-term outcome of 239 APL patients who were

Expression of CD56 has recently been introduced as one of the adverse prognostic factors in acute promyelocytic leukemia (APL). However, the clinical significance of CD56 antigen in APL has not been well elucidated. We assessed the clinical significance of CD56 antigen in 239 APL patients prospectively treated with all-trans retinoic acid and chemotherapy according to the Japan Adult Leukemia Study Group APL97 protocol. All patients were prospectively treated by the Japan Adult Leukemia Study Group APL97 protocol. The median follow-up period was 8.5 years. Positive CD56 expression was found in 23 APL patients (9.6%). Expression of CD56 was significantly associated with lower platelet count ( $P = 0.04$ ), severe disseminated intravascular coagulation ( $P = 0.04$ ), and coexpression of CD2 ( $P = 0.03$ ), CD7 ( $P = 0.04$ ), CD34 ( $P < 0.01$ ) and/or human leukocyte antigen-DR ( $P < 0.01$ ). Complete remission rate and overall survival were not different between the two groups. However, cumulative incidence of relapse and event-free survival (EFS) showed an inferior trend in CD56<sup>+</sup> APL ( $P = 0.08$  and  $P = 0.08$ , respectively). Among patients with initial white blood cell counts of  $3.0 \times 10^9/L$  or more, EFS and cumulative incidence of relapse in CD56<sup>+</sup> APL were significantly worse (30.8% vs 63.6%,  $P = 0.008$ , and 53.8% vs 28.9%,  $P = 0.03$ , respectively), and in multivariate analysis, CD56 expression was an unfavorable prognostic factor for EFS ( $P = 0.04$ ). In conclusion, for APL with higher initial white blood cell counts, CD56 expression should be regarded as an unfavorable prognostic factor.

prospectively treated with ATRA combined with chemotherapies, including anthracycline and Ara-C, in the JALSG APL97 study, and assessed the clinical significance of CD56 expression in APL.

## Materials and Methods

**Patients.** Adult patients with previously untreated APL were consecutively registered to the JALSG APL97 study between May 1997 and June 2002.<sup>(15)</sup> Eligibility criteria were: (i) diagnosis of APL with t(15,17) and/or the *PML-RARA* fusion gene amplified by RT-PCR; (ii) age between 15 and 70 years; (iii) ECOG PS 0 to 3; and (iv) sufficient functioning of the heart, lung, liver, and kidney. This study was approved by the

**Table 1.** Clinical features of acute promyelocytic leukemia (APL) patients according to CD56 expression (*n* = 239)

Clinical features	CD56-positive		CD56-negative		P-value
	No. of patients (%)	Median (range)	No. of patients (%)	Median (range)	
<i>All patients</i>					
No. of patients	23		216		
Age, years		48 (16–66)		47 (15–70)	0.84
15–59	20 (87)		181 (84)		0.69
60–65	3 (13)		35 (16)		
Sex					0.07
Male	9 (39)		127 (59)		
Female	14 (61)		89 (41)		
Initial WBC counts, $\times 10^9/L$		2.1 (0.04–98)		1.7 (0.01–257)	0.47
<3.0	12 (52)		129 (60)		0.78
3.0 to <10.0	6 (26)		46 (21)		
$\geq 10.0$	5 (22)		41 (19)		
Initial APL cell counts, $\times 10^9/L$		1.8 (0–92)		0.6 (0–253)	0.53
Initial platelet counts, $\times 10^9/L$		15 (6–120)		30 (2–238)	0.04
<10	5 (22)		28 (13)		0.30
10 to <40	13 (56)		111 (51)		
$\geq 40$	5 (22)		77 (36)		
ECOG performance status score					0.05
0–2	19 (83)		202 (94)		
3	4 (17)		13 (6)		
Albumin level, g/dL		4.2 (3.3–6.1)		4.2 (2.3–6.0)	0.51
<3.5	2 (9)		18 (9)		0.96
$\geq 3.5$	20 (91)		188 (91)		
Fibrinogen level, mg/dL		105 (55–389)		139 (20–513)	0.46
FDP ratio†		16.1 (4.0–322.4)		11.6 (0.3–524)	0.09
DIC score‡					0.04
0–2	0 (0)		18 (9)		
3–9	17 (77)		166 (82)		
$\geq 10$	5 (23)		18 (9)		
FAB subtype					0.32
Typical	23 (100)		201 (93)		
Variant	0 (0)		15 (7)		
ACAs	8 (42)		64 (35)		0.56
<i>Patients with initial WBC counts <math>\geq 3.0 \times 10^9/L</math></i>					
No. of patients	11		87		
Age, years		41 (21–66)		45 (19–58)	0.87
15–59	10 (91)		73 (84)		0.54
60–65	1 (9)		14 (16)		
Sex					0.81
Male	7 (64)		52 (60)		
Female	4 (36)		35 (40)		
Initial WBC counts, $\times 10^9/L$		6.3 (3.2–98)		8.9 (3.0–257)	0.62
$\geq 10.0$	5 (45)		41 (47)		0.92
Initial APL cell counts, $\times 10^9/L$		4.8 (0–92)		7.0 (0.2–253)	0.37
Initial platelet counts, $\times 10^9/L$		14 (6–54)		23 (2–92)	0.38
<10	3 (30)		16 (18)		0.78
10 to <40	5 (40)		46 (53)		
$\geq 40$	3 (30)		25 (29)		
ECOG performance status score					0.45
0–2	0 (0)		77 (90)		
3	11 (100)		9 (10)		
Albumin level, g/dL		4.3 (3.5–4.7)		4.2 (2.6–5.8)	0.86
<3.5	2 (9)		8 (10)		0.29
$\geq 3.5$	20 (91)		76 (90)		
Fibrinogen level, mg/dL		104 (56–389)		104 (21–438)	0.84
FDP ratio†		26.7 (4.4–280)		14.1 (0.3–303)	0.24
DIC score‡					

Table 1 (continued)

Clinical features	CD56-positive		CD56-negative		P-value
	No. of patients (%)	Median (range)	No. of patients (%)	Median (range)	
0–2	0 (0)		3 (4)		0.02
3–9	7 (64)		75 (88)		
≥10	4 (36)		7 (8)		
FAB subtype					0.17
Typical	11 (100)		74 (85)		
Variant	0 (0)		13 (15)		
ACAs	2 (25)		22 (30)		0.76

†Fibrinogen degradation product (FDP) ratio calculated by dividing the FDP value by its upper normal limit. ‡Disseminated intravascular coagulation (DIC) score:<sup>(18)</sup> 0–2 indicates improbable DIC; score 3, suspected DIC; score 4–9, definitive DIC; ≥10, severe DIC. ACAs, additional chromosomal abnormalities; APL, Acute promyelocytic leukemia; ECOG, Eastern Cooperative Oncology Group; FAB, French–American–British; FDP, fibrin degradation product; WBC, white blood cell.

institutional review boards of each participating institution, and registered with the UMIN Clinical Trials Registry (<http://www.umin.ac.jp/ctrj/>) under trial number C000000206. Informed consent was obtained from each patient before registration to the study in accordance with the Declaration of Helsinki.

**Study design and treatments.** The detail of treatment schedule was as described previously.<sup>(15)</sup> Remission induction therapy consisted of ATRA and chemotherapy with idarubicin and Ara-C, with dose and duration determined by initial WBC counts. After obtaining CR and receiving three courses of intensive consolidation chemotherapy including anthracyclines, Ara-C, and etoposide, patients negative for the *PML-RARA* fusion transcript were randomly allocated either to receive six courses of intensified maintenance chemotherapy or to observation. Patients who were positive for the *PML-RARA* fusion transcript received late ATRA therapy followed by maintenance therapy, and were scheduled to receive allogeneic hematopoietic stem cell transplantation, if they had a human leukocyte antigen-identical donor. Risk stratification according to initial WBC counts ( $<3.0 \times 10^9/L$ ;  $3.0 \times 10^9/L$  to less than  $10.0 \times 10^9/L$ ;  $\geq 10.0 \times 10^9/L$ ) used in the current JALSG APL study are based on the results of the JALSG APL92 study.<sup>(3)</sup> In consideration of this background and the number of cases in each group, we adopted the value and divided the patients into two groups (i.e., initial WBC counts  $<3.0 \times 10^9$  and  $\geq 3.0 \times 10^9$ ) to analyze the prognostic impact of CD56 expression.

**Immunophenotypic analysis.** Immunophenotypic analysis was carried out using bone marrow samples taken at diagnosis and analyzed in the reference laboratory by standard immunofluorescence methods. Cells were stained with anti-CD45 (mAb), gated by CD45 expression and analyzed by flow cytometer. Cells were additionally stained with fluorescein-conjugated mAb against CD2, CD5, CD7, CD4, CD8, CD19, CD20, CD11b, CD13, CD14, CD15, CD33, CD34, CD56, and HLA-DR surface antigens. According to the criteria defined by the European Group for the Immunological Characterization of Leukemias,<sup>(16)</sup> surface markers were defined as positive if more than 20% of APL cells expressed a specific antigen.

**Definition and evaluation of patients.** Hematological response was evaluated by standard criteria.<sup>(17)</sup> Molecular relapse detected by RT-PCR analysis of *PML-RARA* was also considered as a relapse. Overall survival was calculated from the first day of therapy to death or last visit. Event-free survival was

determined from the first day of therapy to relapse, death from any cause, or last visit. Cumulative incidence of relapse (extramedullary relapse) was measured from the date of CR to the first relapse, whereas non-relapse mortality was censored as a competing risk event.

**Statistical analysis.** Categorical data were compared using the  $\chi^2$ -test or Fisher's exact test. Continuous data were compared using Wilcoxon's rank-sum test. The OS and EFS were estimated by Kaplan–Meier methods and compared by the log-rank test. The CIR was analyzed according to Kalbfleisch and Prentice, and differences were compared using Gray statistics. Cox's proportional hazards model was used for multivariate analysis of EFS. Factors significant at the 0.2 level in the univariate analysis were included in the multivariate analysis model. Statistical analyses were carried out using spss version 11.0 (SPSS Inc., Chicago, IL, USA) and R 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria; available at <http://www.r-project.org/>). All hypothesis testing was two-tailed with a significance level of 0.05.

## Results

**Patient characteristics.** Among 283 evaluable patients of 302 registered to the JALSG APL97 study,<sup>(15)</sup> 239 (85%) (median age, 48 years; range, 15–70 years) had satisfactory data for CD56 surface antigen expression, and were evaluated in this study. The median follow-up period was 8.5 years (0–12.2 years).

Of 239 patients, 23 (9.6%) were positive for CD56. The clinical and biological characteristics according to CD56 expression are shown in Tables 1 and 2. Expression of CD56 was significantly associated with lower platelet count ( $<10 \times 10^9/L$ ) and severe DIC ( $P = 0.04$  and  $P = 0.04$ , respectively); CD56<sup>+</sup> APL significantly coexpressed CD2, CD7, CD34, and/or HLA-DR antigen. ( $P = 0.03$ ,  $P = 0.04$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively).

**Treatment outcome.** The CR rate and incidence of early death during induction therapy were not different between CD56<sup>+</sup> and CD56<sup>-</sup> APL (91% vs 95%,  $P = 0.4$ , and 9% vs 5%,  $P = 0.54$ , respectively; Table 3). Primary resistance to induction therapy was not observed in either group. The incidence of differentiation syndrome was not different between the two groups (22% vs 21%,  $P = 0.9$ ; Table 3).

Overall survival was not different between the two groups (73.9% vs 79.2%,  $P = 0.52$ , at 9 years; Fig. 1a), whereas EFS

**Table 2. Immunophenotypic features of acute promyelocytic leukemia patients (*n* = 239) according to CD56 expression**

Parameters	CD56-positive No. of patients (%)	CD56-negative No. of patients (%)	<i>P</i> -value
CD2			
Positive	5 (22)	16 (8)	0.03
Negative	18 (78)	191 (92)	
CD5			
Positive	1 (5)	3 (2)	0.25
Negative	18 (95)	195 (98)	
CD7			
Positive	2 (9)	4 (2)	0.04
Negative	20 (91)	208 (98)	
CD19			
Positive	1 (4)	5 (2)	0.56
Negative	22 (96)	210 (98)	
CD20			
Positive	0 (0)	1 (0.5)	0.75
Negative	19 (100)	191 (99.5)	
CD11b			
Positive	3 (19)	11 (7)	0.08
Negative	13 (81)	157 (93)	
CD15			
Positive	7 (54)	50 (33)	0.12
Negative	6 (46)	103 (67)	
CD41a			
Positive	1 (5)	19 (10)	0.46
Negative	20 (95)	177 (90)	
CD34			
Positive	9 (41)	27 (13)	<i>P</i> < 0.01
Negative	13 (59)	185 (87)	
HLA-DR			
Positive	7 (30)	16 (8)	<i>P</i> < 0.01
Negative	16 (70)	197 (92)	

HLA, human leukocyte antigen.

and CIR tended to be inferior in CD56<sup>+</sup> APL (47.8% vs 64.8%, *P* = 0.08, and 39.1% vs 24.3%, *P* = 0.08, at 9 years, respectively; Figs 2a,3a). In patients with initial WBC counts  $\geq 3.0 \times 10^9/L$ , EFS and CIR for 11 CD56<sup>+</sup> APL patients were significantly inferior to those for 87 CD56<sup>-</sup> APL patients (30.8% vs 63.6%, *P* = 0.008, and 53.8% vs 28.9%, *P* = 0.03, at 9 years, respectively; Figs 2b,3b). In patients with initial WBC counts  $< 3.0 \times 10^9/L$ , EFS and CIR were not different between the two groups (*P* = 0.99 and *P* = 0.98, at 9 years, respectively). The OS in patients with initial WBC counts  $\geq 3.0 \times 10^9/L$  was similar between the two groups (61.5% vs 78.8%, *P* = 0.13, at 9 years; Fig. 1b). Although the number was small, EFS and CIR for five CD56<sup>+</sup> APL patients among those with initial WBC counts of  $\geq 10 \times 10^9/L$  were inferior to those for 41 CD56<sup>-</sup> APL patients (20.0% vs 60.9%, *P* = 0.03, and 60.0% vs 30.7%, *P* = 0.09, at 9 years, respectively). Cumulative incidence of extramedullary relapse tended to be more frequent in patients with CD56<sup>+</sup> APL whose initial WBC counts were  $\geq 3.0 \times 10^9/L$  (9.3% vs 1.1%, at 9 years, *P* = 0.07). We also analyzed the influence of CD56 expression on clinical outcomes according to Sanz's relapse risk score.<sup>(7)</sup> Both CIR and EFS in patients with CD56<sup>+</sup> APL were inferior in the high risk group (60.0% vs 31.4%, *P* = 0.09 and 20.0% vs 62.5%, *P* = 0.02, respectively), but not in low and intermediate risk groups (*P* = 0.17 and *P* = 0.55, respectively).

**Table 3. Clinical outcomes of acute promyelocytic leukemia patients according to CD56 expression (*n* = 239)**

Clinical features	CD56- positive	CD56- negative	<i>P</i> -value
	No. of patients (%)	No. of patients (%)	
No. of patients	23	216	
Induction outcome			
CR rate	21 (91)	206 (95)	0.40
Differentiation syndrome	5 (22)	44 (21)	0.90
Induction death	2 (9)	10 (5)	0.54
Hemorrhage	2 (100)	6 (60)	0.13
Infection	0 (0)	1 (10)	0.74
Differentiation syndrome	0 (0)	2 (20)	0.64
Others	0 (0)	1 (10)	0.74
Postremission outcome			
No. of patients	21	206	
Relapse			
All patients	9 (43)	49 (24)	0.06
Initial WBC counts $< 3.0$	3 (14)	27 (13)	0.88
Initial WBC counts $\geq 3.0$	6 (29)	22 (11)	0.02
Extramedullary relapse			
All patients	1 (5)	3 (1.5)	0.27
Initial WBC counts $< 3.0$	0 (0)	2 (1.0)	0.65
Initial WBC counts $\geq 3.0$	1 (5)	1 (0.5)	0.05
CIR (%)			
All patients	39.1	24.3	0.08
Initial WBC counts $< 3.0$	20.0	20.1	0.98
Initial WBC counts $\geq 3.0$	53.8	28.9	0.03
CIR (extramedullary relapse) (%)			
All patients	5.0	1.5	0.27
Initial WBC counts $< 3.0$	0.0	1.8	0.69
Initial WBC counts $\geq 3.0$	9.3	1.1	0.07

CIR, cumulative incidence of relapse; CR, complete remission; WBC, white blood cell.

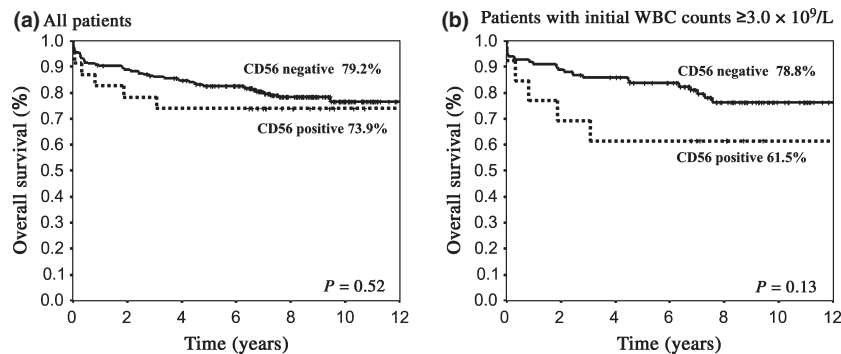
In the multivariate analysis, CD56 expression was an independent adverse prognostic factor for EFS in patients whose initial WBC counts were  $\geq 3.0 \times 10^9/L$  (hazard ratio = 2.54; 95% confidence interval, 1.07–6.06, *P* = 0.04) (Table 4).

## Discussion

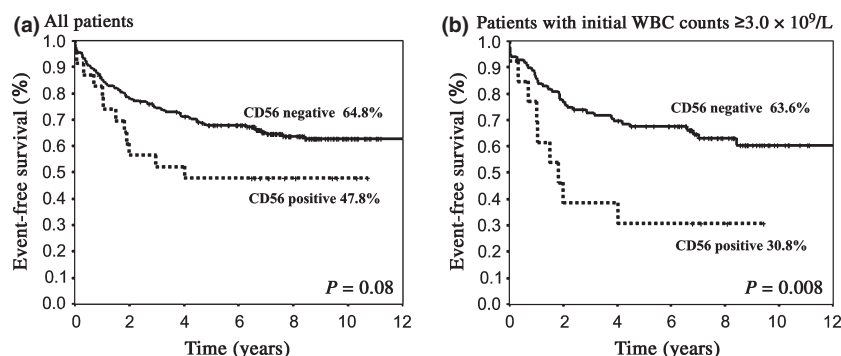
Expression of CD56 has been reported as one of the adverse prognostic factors in AML with t(8;21), associated with a short remission duration and survival as well as higher incidence of extramedullary relapse.<sup>(19,20)</sup> Recently, several investigators have suggested that CD56 expression is also associated with short remission duration in APL, higher CIR, and extramedullary relapse (Table 5).<sup>(9–12)</sup> However, large-scale studies with long-term follow-up are limited,<sup>(12)</sup> and the prognostic significance of CD56 expression has not been fully elucidated.

Our study, analyzing 239 APL patients, showed a significant correlation between CD56 expression with lower platelet counts and severe DIC. In contrast to previous reports,<sup>(9,10,12)</sup> CD56 expression was not associated with higher WBC counts, lower albumin levels, or higher frequency of M3 variant. Severity of DIC was related to platelet counts in CD56<sup>+</sup> APL,

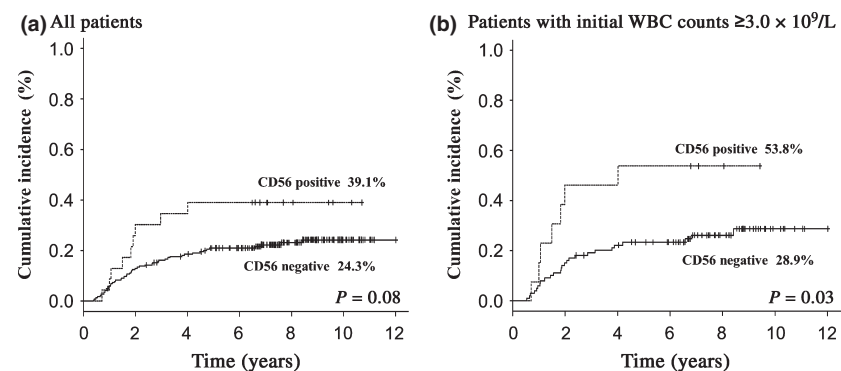
**Fig. 1.** Overall survival (OS) of patients with acute promyelocytic leukemia according to CD56 expression. (a) OS was not different between the two groups for all patients (73.9% vs 79.2% at 9 years,  $P = 0.52$ ). (b) In patients whose white blood cell (WBC) count was  $\geq 3.0 \times 10^9/L$ , OS did not differ between the two groups (61.5% vs 78.8%,  $P = 0.13$ ).



**Fig. 2.** Event-free survival (EFS) of patients with acute promyelocytic leukemia (APL) according to CD56 expression. (a) EFS for all patients showed an inferior trend in CD56<sup>+</sup> APL (47.8% vs 64.8% at 9 years,  $P = 0.08$ ). (b) In patients whose white blood cell (WBC) count was  $\geq 3.0 \times 10^9/L$ , EFS for CD56<sup>+</sup> APL was significantly inferior to that for CD56<sup>-</sup> APL (30.8% vs 63.6%,  $P = 0.008$ ).



**Fig. 3.** Cumulative incidence of relapse (CIR) of patients with acute promyelocytic leukemia (APL) according to CD56 expression. (a) CIR for all patients showed an inferior trend in the CD56<sup>+</sup> APL group (39.1% vs 24.3% at 9 years,  $P = 0.08$ ). (b) In patients whose white blood cell (WBC) count was  $\geq 3.0 \times 10^9/L$ , CIR for the CD56<sup>+</sup> group was significantly higher compared to that for the CD56<sup>-</sup> APL group (53.8% vs 28.9%,  $P = 0.03$ ).



although fibrinogen levels and fibrinogen degradation product ratios (fibrinogen degradation product value/its upper limit of normal value) were not different (Table 1). The relationship between CD56 expression and DIC in AML, including APL, has not been elucidated. As statistically significant findings associated with CD56<sup>+</sup> APL in previous reports were not the same as our present study, further studies with sufficient numbers of patients will be needed to clarify the characteristic features of CD56<sup>+</sup> APL.

Consistent with the report from the PETHEMA/HOVON group,<sup>(12)</sup> CD56<sup>+</sup> APL cells frequently coexpressed CD2, CD7, CD34, and/or HLA-DR antigen in our study. Although the mechanism leading to aberrant expression of lymphoid markers, such as CD2 and CD7 in CD56<sup>+</sup> APL cells, remains unclear, the expression of these antigens, as well as CD34 and HLA-DR, may indicate that CD56<sup>+</sup> APL cells arise in more immature, undifferentiated, and progenitor cells, as previously suggested in acute leukemia.<sup>(21)</sup>

The PETHEMA/HOVON group have reported lower CR rates in their patients with CD56<sup>+</sup> APL.<sup>(12)</sup> However, our study showed no difference in CR and induction mortality rates. Their patients with CD56<sup>+</sup> APL showed poorer ECOG PS scores and lower albumin levels compared with our patients. Higher ECOG PS scores and lower albumin levels were reportedly associated with induction mortality.<sup>(22)</sup> Therefore, the difference may be explained by the characteristics of patients enrolled in both studies.

Our study indicated that CD56 expression was correlated with higher CIR and inferior EFS, and was an independent adverse prognostic factor for EFS by multivariate analysis among APL patients whose initial WBC counts were  $\geq 3.0 \times 10^9/L$ . These results verified that CD56 expression was one of the adverse prognostic factors in APL patients. However, the direct molecular mechanism why CD56 expression in APL is associated with poor prognosis still remains unclear. CD56 expression is reportedly associated with higher



expression of P-glycoprotein in AML<sup>(23,24)</sup> but their adverse prognostic roles seem independent.<sup>(24)</sup> Unfortunately, neither ours nor other studies focusing on CD56<sup>+</sup> APL have tested the association between CD56 and P-glycoprotein. However, APL expressing CD34 was reportedly less sensitive to ATRA therapy.<sup>(25,26)</sup> Therefore, coexpression of CD34 antigen might explain the higher CIR in CD56<sup>+</sup> APL, although the RT-PCR negativity after the consolidation chemotherapy was not different between CD56<sup>+</sup> and CD56<sup>-</sup> APL.

In this study, CD56 expression was not determined as one of the prognostic factors in APL patients whose initial WBC counts were  $<3.0 \times 10^9/L$ . One explanation might be that it has become difficult to determine significant risk factors in patients with APL, whose prognosis has considerably improved.<sup>(1-5)</sup> In particular, in patients with lower initial WBC counts, the outcome has been dramatically improved in the ATRA era.<sup>(3,27)</sup> Another considerable reason is that there might be synergistic action between CD56 expression and some undetermined proliferation molecular factors. Additionally, extramedullary relapse, observed frequently in patients with CD56<sup>+</sup> APL whose initial WBC counts are  $\geq 3.0 \times 10^9/L$ , might also be a reason. The molecular mechanism behind why CD56<sup>+</sup> APL patients with higher initial WBC counts show poor prognosis should be clarified in a future study.

Recently, arsenic trioxide, gemtuzumab ozogamicin, and tamibarotene have been shown to be effective for APL,<sup>(28-33)</sup> and, in fact, most of our relapsed patients received these drugs as well as stem cell transplantation. This may be a plausible reason why EFS and CIR tended to be worse in CD56<sup>+</sup> APL, but not OS, because these drugs and transplantation salvaged the relapsed patients.

Although our study confirmed CD56 expression as an independent adverse prognostic factor in APL patients with higher initial WBC counts who were treated with ATRA and chemotherapy (Table 4), the clinical significance of CD56 expression might change with the introduction of more potent agents as front-line therapy. Expression of CD56 has not been included so far in standard treatments recommended by the European LeukemiaNet.<sup>(14)</sup> However, some recent

**Table 4. Prognostic factors affecting event-free survival of acute promyelocytic leukemia patients (initial white blood cell counts  $\geq 3.0 \times 10^9/L$ ) (n = 239)**

Factors for event-free survival	Univariate analysis		Multivariate analysis	
	P-value	Hazard ratio	95% CI	P-value
DIC score $>10$ (vs DIC score $\leq 10$ )	0.17	1.06	0.90–1.24	0.48
Age $>60$ years (vs age $\leq 60$ years)	0.04	2.00	0.86–4.65	0.11
HLA-DR antigen positive (vs negative)	0.02	1.46	0.49–4.33	0.49
CD56 antigen positive (vs negative)	0.008	2.54	1.07–6.06	0.04

†Disseminated intravascular coagulation (DIC) score:<sup>(18)</sup> 0–2 indicates improbable DIC; score 3, suspected DIC; score 4–9, definitive DIC;  $\geq 10$ , severe DIC. Factors with P-value  $<0.20$  in univariate analysis were included in the multivariate analysis. CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio.

**Table 5. Clinical features and outcomes in acute promyelocytic leukemia (APL) patients with CD56 expression, as reported in published works**

Authors	No. of patients	Treatment	CD56 <sup>+</sup> APL (%)	Clinical features in patients with CD56 <sup>+</sup> APL*	CR rate		CIR		CIR (extramedullary)		DFS†		OS	
					CD56 <sup>+</sup>	CD56 <sup>-</sup>	CD56 <sup>+</sup>	CD56 <sup>-</sup>	CD56 <sup>+</sup>	CD56 <sup>-</sup>	CD56 <sup>+</sup>	CD56 <sup>-</sup>	CD56 <sup>+</sup>	CD56 <sup>-</sup>
Murray et al. <sup>(9)</sup>	50	CT alone / ATRA alone / ATRA + CT	24%	S-isoform†, Fibrinogen‡	50%*	84%	NA	NA	NA	NA	NA	NA	5 weeks*	232 weeks
Ferrara et al. <sup>(10)</sup>	100	ATRA + CT	15%	No effect	87%	94%	NA	NA	13%	8%	22 months	NR	62%*	86%
Ito et al. <sup>(11)</sup>	28	ATRA + CT	14%	Coexpression of CD34	100%	87%	NA	NA	75%*	0%	4 months*	NR	26 months	NR
Montesinos et al. <sup>(12)</sup>	651	CT alone / ATRA + CT	11%	Initial WBC counts†, Albumin‡, S-isoform†, Coexpression of CD2, CD7, CD15, CD34, CD117, and HLA-DR	85%	92%	22%*	10%	7%*	1%	73%*	85%	78%	84%
Present study (all patients)	225	ATRA + CT	10%	Initial platelet counts‡, Severe DIC†, Coexpression of CD2, CD7, CD34, and HLA-DR	91%	95%	39%	24%	5%	1.5%	48%	65%	74%	79%
Present study (initial WBC counts $\geq 3.0 \times 10^9/L$ )	112	ATRA + CT	12%		92%	94%	54%*	29%	9.3%	1.1%	31%*	64%	62%	79%

\*Significant difference. †Event-free survival in present study. APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; CIR, cumulative incidence of relapse; CR, complete remission; CT, chemotherapy; DFS, disease-free survival; DIC, disseminated intravascular coagulation; HLA, human leukocyte antigen; NA, not available; NR, not reached; OS, overall survival; WBC, white blood cell.

published research, including ours (summarized in Table 5), will promote the modification of treatment for CD56<sup>+</sup> APL. In fact, it is proposed in some recently published studies. We should not only continue to monitor CD56 expression in APL patients, but use more effective therapeutic strategies for patients with CD56<sup>+</sup> APL, especially those with higher initial WBC counts.

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## Disclosure Statement

The authors have no conflict of interest.

## Abbreviations

AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
Ara-C	cytosine arabinoside
ATRA	all-trans retinoic acid
CIR	cumulative incidence of relapse
CR	complete remission
DIC	disseminated intravascular coagulation
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
HLA	human leukocyte antigen
HOVON	Hemato-Oncologie voor Volwassenen Nederland
JALSG	Japan Adult Leukemia Study Group
OS	overall survival
PETHEMA	Programa de Estudio y Tratamiento de las Hemopatías Malignas
PS	performance status
WBC	white blood cell

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