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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This study was registered with the UMIN Clinical Trials Registry (http://www.umin.ac.jp ctrj/) under trial number: C00000206.

Funding Information
National Cancer Center Research and Development Fund (23-A-23), Japanese Ministry of Health, Labor and Welfare (Clinical Cancer Research 23-004 and 25100501). Project for Development of Innovative on Cancer Therapeutics (P-Direct).

Received May 7, 2013; Revised October 28, 2013; Accepted October 31, 2013

Cancer Sci 105 (2014) 97–104
doi: 10.1111/cas.12319

The clinical introduction of ATRA has dramatically improved the outcome of APL.1–6 However, 13–33% of patients with APL still relapse after the first remission.6 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.3,5–8 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.9–12 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.13,14 We analyzed the long-term outcome of 239 APL patients who were 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 2002.15 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                        | 23            | 216           |         |
| Age, years                             |               |               |         |
| 15-59                                  | 20 (87)       | 181 (84)      | 0.69    |
| 60-65                                  | 3 (13)        | 35 (16)       |         |
| Sex                                    |               |               |         |
| Male                                   | 9 (39)        | 127 (59)      | 0.07    |
| Female                                 | 14 (61)       | 89 (41)       |         |
| Initial WBC counts, ×10^9/L            |               |               |         |
| <3.0                                   | 12 (52)       | 129 (60)      | 0.78    |
| 3.0 to <10.0                           | 6 (26)        | 46 (21)       |         |
| ≥10.0                                  | 5 (22)        | 41 (19)       |         |
| Initial APL cell counts, ×10^9/L       |               |               |         |
| <10                                    | 5 (22)        | 28 (13)       | 0.30    |
| 10 to <40                              | 13 (56)       | 111 (51)      |         |
| ≥40                                    | 5 (22)        | 77 (36)       |         |
| ECOG performance status score          |               |               |         |
| 0-2                                    | 19 (83)       | 202 (94)      | 0.05    |
| 3                                      | 4 (17)        | 13 (6)        |         |
| Albumin level, g/dL                    |               |               |         |
| <3.5                                   | 2 (9)         | 18 (9)        | 0.96    |
| ≥3.5                                   | 20 (91)       | 188 (91)      |         |
| Fibrinogen level, mg/dL                |               |               |         |
| FDP ratio†                             | 16.1 (4.0–322.4) | 11.6 (0.3–524) | 0.09   |
| DIC score‡                             |               |               |         |
| 0-2                                    | 0 (0)         | 18 (9)        | 0.04    |
| 3                                      | 17 (77)       | 166 (82)      | 0.81    |
| FAB subtype                            |               |               |         |
| Typical                                | 23 (100)      | 201 (93)      | 0.32    |
| Variant                                | 0 (0)         | 15 (7)        |         |
| ACAs                                   | 8 (42)        | 64 (35)       | 0.56    |

Patients with initial WBC counts ≥3.0 × 10^9/L

| 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) | 0.81 |
| Sex             |     |     |
| Male            | 7 (64) | 52 (60) | 0.81 |
| Female          | 4 (36) | 35 (40) |       |
| Initial WBC counts, ×10^9/L              |     |     |
| ≥10.0           | 5 (45) | 41 (47) | 0.62 |
| Initial APL cell counts, ×10^9/L         |     |     |
| <10             | 3 (30) | 16 (18) | 0.78 |
| 10 to <40       | 5 (40) | 46 (53) | 0.37 |
| ≥40             | 3 (30) | 25 (29) | 0.38 |
| ECOG performance status score             |     |     |
| 0-2             | 0 (0) | 77 (90) | 0.45 |
| 3               | 11 (100) | 9 (10) |     |
| Albumin level, g/dL                        |     |     |
| <3.5            | 2 (9) | 8 (10) | 0.29 |
| ≥3.5            | 20 (91) | 76 (90) |     |
| Fibrinogen level, mg/dL                    |     |     |
| FDP ratio†     |     |     |
| DIC score‡     |     |     |
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. 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 cycles 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 CD56 surface antigen expression, and were evaluated in this study. The median follow-up period was 8.5 years (0–12.2 years).

**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, 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. 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 χ²-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 ssrs 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, (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 × 10⁹/L) and severe DIC (P = 0.04 and P = 0.04, respectively); CD56+ 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− and CD56+ 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 1 (continued)

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

1Fibrinogen degradation product (FDP) ratio calculated by dividing the FDP value by its upper normal limit. 2Disseminated intravascular coagulation (DIC) score: 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.
and CIR tended to be inferior in CD56+ 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 ≥3.0 × 10^9/L, EFS and CIR for 41 CD56+ APL patients were significantly inferior to those for 87 CD56- APL patients (30.8% vs 63.6%, P = 0.008, and 28.9% vs 39.1%, P = 0.03, at 9 years, respectively; Figs 2b,3b). In patients with initial WBC counts <3.0 × 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 ≥3.0 × 10^9/L was similar between the two groups (61.5% vs 78.8%, P = 0.17, at 9 years; Fig. 1b). Although the number was small, EFS and CIR for five CD56+ APL patients among those with initial WBC counts of ≥10 × 10^9/L were inferior to those for 41 CD56- 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+ APL whose initial WBC counts were ≥3.0 × 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.7 Both CIR and EFS in patients with CD56+ 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).

In the multivariate analysis, CD56 expression was an independent adverse prognostic factor for EFS in patients whose initial WBC counts were ≥3.0 × 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.19,20 Recently, several investigators have suggested that CD56 expression is also associated with short remission duration in APL, higher CIR, and extramedullary relapse (Table 5).9-12 However, large-scale studies with long-term follow-up are limited,12 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,9,10,12 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+ APL,
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+ 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+ APL.

Consistent with the report from the PETHEMA/HOVON group, CD56+ 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+ APL cells, remains unclear, the expression of these antigens, as well as CD34 and HLA-DR, may indicate that CD56+ APL cells arise in more immature, undifferentiated, and progenitor cells, as previously suggested in acute leukemia. The PETHEMA/HOVON group have reported lower CR rates in their patients with CD56+ APL. However, our study showed no difference in CR and induction mortality rates. Their patients with CD56+ 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. 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 (23,24) but their adverse prognostic roles seem independent (24). Unfortunately, neither ours nor other studies focusing on CD56+ APL have tested the association between CD56 and P-glycoprotein. However, APL expressing CD34 was reportedly less sensitive to ATRA therapy (25,26). Therefore, coexpression of CD34 antigen might explain the higher CIR in CD56+ APL, although the RT-PCR negativity after the consolidation chemotherapy was not different between CD56+ and CD56− APL.

In this study, CD56 expression was not determined as one of the prognostic factors in APL patients whose initial WBC counts were \( \geq 3.0 \times 10^9/L \). One explanation might be that it has become difficult to determine significant risk factors in patients with APL, whose prognosis has considerably improved (11–15). In particular, in patients with lower initial WBC counts, the outcome has been dramatically improved in the ATRA era (3,27). 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+ APL whose initial WBC counts are \( \geq 3.0 \times 10^9/L \), might also be a reason. The molecular mechanism behind why CD56+ 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 (28–33) 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+ 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 (14). 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 \( \leq 60 \)) | 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 |

1Disseminated intravascular coagulation (DIC) score, \( 0–2 \) 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.
published research, including ours (summarized in Table 5), will promote the modification of treatment for CD56+ 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+ APL, especially those with higher initial WBC counts.

Acknowledgments

We thank the participating patients for consenting to enter this study and the participating physicians from 92 institutions who registered their patients and provided necessary data. We are deeply grateful to Drs. Miki Nishimura, Tohru Kobayashi, and Motohiro Tsuzuki for their assistance in designing the protocol. Dr. Hiroyuki Fujita updated collected data in March 2010. Dr. Ryuzo Ohno reviewed the manuscript. This work was supported in part by the National Cancer Center Research and Development Fund (23-A-23), Grants-in-Aid from the Japanese Ministry of Health, Labor and Welfare (Clinical Cancer Research 23-004 and 25100501), and Grants-in-Aid from the Project for Development of Innovative on Cancer Therapeutics (F- Direct).

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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