The biological characteristics of CD34$^+$ CD2$^+$ adult acute promyelocytic leukemia and the CD34$^-$ CD2$^-$ hypergranular (M_3) and microgranular (M_{3v}) phenotypes

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Background and Objectives. Acute promyelocytic leukemia (APL) is characterized by leukemic cells blocked at the promyelocytic stage of granulocytic differentiation. To date, it is still not clear whether CD34 expression identifies a subset of APL patients with peculiar characteristics. We, therefore, conducted a detailed analysis of CD34 expression at diagnosis in 136 adults with *de novo* APL.

Design and Methods. We investigated 136 newly diagnosed APL patients from four Italian Institutions. All 136 cases were tested for CD34 and CD2 expression: 124 (91%) cases were classified as hypergranular (M3) and 12 (9%) as the hyporgranular M3 variant (M_{3v}). The parameters considered were white blood cell (WBC) and platelet counts, hemoglobin levels, percentage of peripheral blood leukemic promyelocytes (PBLP), CD15, CD56 and HLA-DR expression, and the PML/RARα isoform, to assess their relationship with CD34 and CD2 expression.

Results. CD34 expression was associated with the M3v subtype and higher proportion of HLA-DR$^+$ and CD2$^+$ cases. Moreover, compared with CD34$^-$ APL patients, CD34$^+$ APL patients had a significantly higher percentage of PBLP at presentation, were more frequently female and had a higher proportion of bcr3 expression. Among the 136 APL cases, 24 (17.6%) and 80 (58.8%) were identified as CD34$^+$CD2$^+$ and CD34$^-$CD2$^-$, respectively. The two groups showed statistically significant differences in terms of M3v frequency, WBC and platelet counts, percentage of PBLP, and bcr3 expression. Moreover, the CD34$^+$CD2$^+$ group showed a higher proportion of CD34$^+$ and bcr3 isoforms compared to the M_{3v} cases. There were no differences between the two groups in terms of complete remission, overall survival and disease-free survival.

Interpretation and Conclusions. Our findings suggest that immunophenotypic analysis can distinguish a subset of APL patients with different biological characteristics.

Key words: acute promyelocytic leukemia, immunophenotype, CD34, CD2.

Haematologica 2006; 91:311-316

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Acute promyelocytic leukemia (APL) is an acute myeloid leukemia characterized by leukemic cells blocked at the promyelocytic stage of granulocytic differentiation. According to the French-American-British (FAB) classification, two main cytological subtypes are recognized: (i) classical hypergranular promyelocytic leukemia (M_3) and (ii) the microgranular promyelocytic leukemia variant (M_{3v}).[1-4] Recent results from gene expression profiling suggest that the two morphological subtypes of APL, M_3 and M_{3v}, are clearly separable. These studies suggest that the difference may lie in *FLT3*.[5-6] This gene has been found to be mutated more frequently in M_{3v} than in M_3 APL and more frequently in APL with the short (S-, bcr3) rather than the long (L, bcr1) form of PML/RARα transcript form.[7] Low or negative CD34 expression in addition to absent HLA-DR used to be the paradigm of the APL immunophenotype.[8] However, elevated CD34 expression can occur in APL and appears to be associated with leukocytosis, hypogranular morphology and/or the S-form of the PML/RARα transcript.[9-12] Similarly, CD2, a T-lineage affiliated antigen, has been associated with M_{3v} morphology and/or the bcr3 isoform.[13-14] Moreover, a recent study reported that CD34 surface expression is associated with poor clinical outcome in patients with APL.[9] Despite all these data, the issue of CD34 expression in APL remains unsolved because (i) the studies cited above included few APL cases evaluable for CD34 expression; (ii) in the analyzed series the M_3 cases have never been distinguished from the M_{3v} ones; (iii) it is still not clear whether CD34 expression identifies a subset of APL-M3 patients with peculiar characteristics. The aim of our study was to make a detailed analysis of CD34 expression at diagnosis in 136 patients with *de novo* APL in order to determine whether subsets with some discrete biological characteristics could be identified.

Design and Methods

Patients

Between May 1990 and August 2003, 136 newly diagnosed APL patients from four Italian Institutions were treated according to the GIMEMA protocols AIDA[15] (all-trans retinoic acid plus chemotherapy, n=116) and LAP0389[16] (chemotherapy alone, n=4). The remaining 16 patients were treated with idarubicin (n=5) or all-trans retinoic acid (n=6) alone, and cytarabine plus idarubicin (n=5). The median follow-up was 48.2 months (0-149 months). Peripheral blood and bone marrow samples were analyzed. Standard microscopic and cytochemical evaluations were used to classify the morphological subtypes according to the FAB criteria.[1,3] It was found that 124 (91%) had M_3 APL while the remaining 12 (9%) had M_{3v} APL. All cases were confirmed to have t(15;17) by karyotyping or fluorescent *in situ* hybridization (FISH) analysis and PML-RARα by reverse transcriptase polymerase chain reaction (RT-PCR) in 105 cases.

Immunophenotypic analysis

Leukemic cell analysis was performed on bone marrow cells by standard immunofluorescence methods using monoclonal antibodies directed against CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD33, CD34, CD45, CD56, CD117, and HLA-DR (Becton Dickinson). All cases were studied by direct immunofluorescence.

Flow cytometric analysis was performed on a FACScan flow cytometer (Becton Dickinson Immunocytometry System, Mountain View, CA, USA USA). A sample was considered antigen-positive if ≥20% of the leukemic cells reacted with a particular monoclonal antibody. In common with other investigators,[9,11,17] we used a ≥10% cutoff to quantify the presence of a subpopulation of $CD34^+$ cells, as opposed to ≥20%, used for disease characterization.

Response to treatment

Complete remission and relapse were defined using the criteria proposed by the National Cancer Institute-sponsored workshop for acute myeloid leukemia.[18] Molecular relapse (assessed only in the AIDA 0493) was defined as conversion from PCR-negative to PCR-positive for PML/RARα at any time after consolidation therapy confirmed in two successive marrow samples collected 2-4 weeks apart. Patients who died early, before the induction therapy evaluation, and those who underwent palliative treatment were considered as not evaluable for response.

Statistical analysis

The Kolgomorov and Smirnov test was used to assess whether the data sample belonged to a population with a Gaussian distribution. Student's t-test or the Mann-Whitney test was performed for comparisons of means. A two-tailed Fisher's exact test was used to compare categories. Only p values <0.05 were considered to be statistically significant. Overall survival was measured from the time of diagnosis to death or last follow-up visit, whereas disease-free survival was taken as the interval from the date of complete remission to relapse (molecular and/or hematologic), death, or last follow-up. The overall survival and the disease-free survival were calculated using the Kaplan-Meier method. The log-rank test was used to compare survival curves. Patients with bcr-2 transcript (three cases with M3 morphology and $CD34^-CD2^-$ immunophenotype) were excluded from the analysis comparing bcr-1 and bcr-3.

Table 1. The characteristics of $CD34^+$ and $CD34^-$ patients.

	$CD34^+$	$CD34^-$	p
Cases	47	89	
Sex male/female	15/32	45/44	0.04
Age (min-max)	35 (18-78)	45 (18-88)	n.s.
M_3/M_{3v}	39/8	85/4	0.02
WBC count ($\times10^9$/L)	5.1 (0.3-147)	2.2 (0.3-109)	n.s
Platelet count ($\times10^9$/L)	23 (4-384)	27(4-159)	n.s.
Hemoglobin (×g/dL)	8.8 (4.5-15.7)	8.7 (1.4-13.3)	n.s.
PBLP %	78 (0-100)	29 (0-100)	0.009
$CD15^+/CD15^-$	12/30	20/38	n.s.
$HLA\text{-}DR^+/DR^-$	11/33	8/78	0.03
$CD56^+/CD56^-$	7/27	10/62	n.s.
$CD2^+/CD2^-$	24/23	9/80	<0.0001
bcr1/bcr3	14/23	48/17	0.0006

PBLP: peripheral blood leukemia promyelocytes.

Results

$CD34^+$ vs $CD34^-$

The main characteristics of the patients according to CD34 expression are detailed in Table 1; among the 136 patients, 47(34.5%) patients were $CD34^+$ (median 31%; range 10%-99%). CD34 expression was associated with the M3v subtype (8[17%] patients vs 4 [4.4%] patients; p=0.02), and a higher proportion of $HLA\text{-}DR^+$ and $CD2^+$ cases (11 [25.5%] vs 8 [10%] patients and 24 [51%] vs 9 [10.1%] patients; p=0.03 and p<0.0001, respectively). Moreover, $CD34^+$ APL patients had a significantly higher percentage of peripheral blood leukemic promyelocytes at presentation (78% vs 29%; p=0.009) compared with $CD34^-$ APL patients, were more likely to be female (32 [68%] vs 44 [49.4%]; p=0.04) and had a higher proportion of

Table 2. The characteristics of CD34+CD2+ and CD34-CD2- patients.

	CD34+CD2+	*CD34-CD2-*	*p*
Cases	24	80	
Sex M/F	9/15	41/39	n.s.
Age (min-max)	33.5 (18-70)	44.5(18-88)	n.s.
M_3/M_{3v}	18/6	80/0	<0.0001
WBC count (×10⁹/L)	9.9 (0.4-147)	1.8 (0.3-109)	0.0004
Platelet count (×10⁹/L)	21 (4-384)	28 (5-159)	0.03
Hemoglobin (×g/dL)	9.1 (4.5-15.7)	8.6 (3.4-13,3)	n.s.
PBLP %	88 (0-100)	28 (0-100)	0.0001
CD15+/CD15-	4/16	17/37	n.s.
HLA-DR+/DR-	5/19	6/71	n.s.
CD56+/CD56-	5/13	9/57	n.s.
bcr1/bcr3	7/15	43/14	0.0006

PBLP: peripheral blood leukemia promyelocytes.

Table 3. The characteristics of CD34+CD2+ and M_{3v} patients.

	CD34+CD2+	*M_{3v}*	*p*
Cases	18	12	
Sex M/F	6/12	4/8	n.s.
Age (min-max)	37.5 (21-70)	33.5 (18-58)	n.s.
CD34+/CD34-	18/0	8/4	0.01
CD2+/CD2-	18/0	10/2	n.s.
WBC count (×10⁹/L)	8.2 (0.4-147)	33.4 (0.8-135)	n.s.
Platelet count (×10⁹/L)	22 (4-83)	14 (4-384)	n.s.
Hemoglobin (× g/dL)	8.8 (4.5-15.7)	9.7 (5.6-11.4)	n.s.
PBLP %	87 (0-100)	93 (10-98)	n.s.
CD15+/CD15-	1/15	5/1	0.001
HLA-DR+/DR-	2/16	6/6	0.03
CD56+/CD56-	4/11	2/6	n.s.
bcr1/bcr3	4/12	7/3	0.04

PBLP: peripheral blood leukemic promyelocytes.

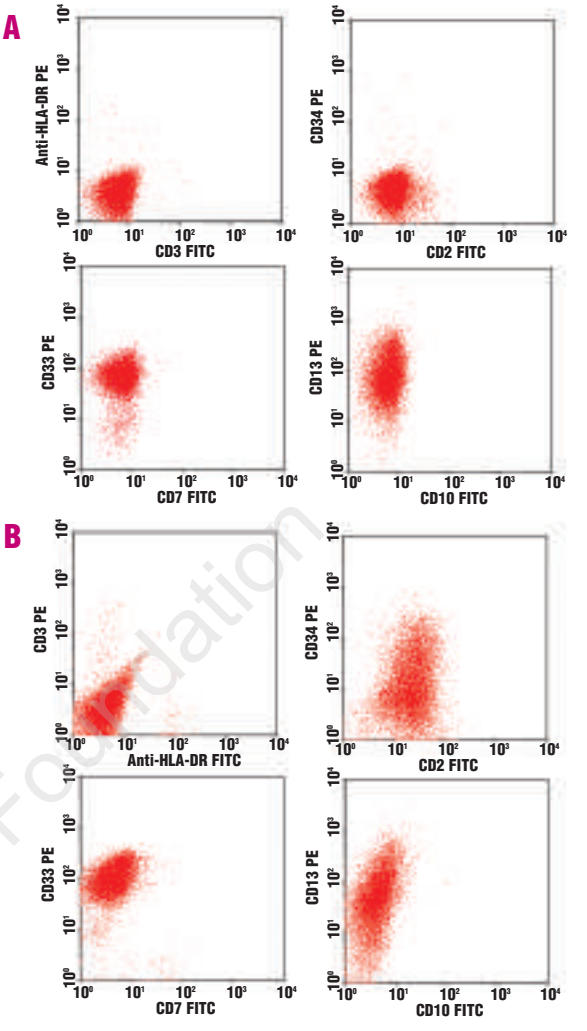

Figure 1. Immunophenotypic analysis of leukemic cell performed on bone marrow cells by immunofluorescence methods using monoclonal antibodies directed against HLA-DR, CD13, CD33, CD34, CD2, CD3, and CD7. A. Classic immunophenotypic pattern shows positive expression for CD13 and CD33 whereas HLA-DR, CD34 and CD2 antigens are negative. B. Concomitant expression of CD34 and CD2 in APL. The leukemic population showed a lineage profile clearly myeloid (CD13+ and CD33+) whereas other lymphoid-lineage affiliated antigens (such as CD7 and CD10) are usually not observed.

bcr3 expression (23 [62%] vs 17 [26.1%]; p=0.0006). However, there were no statistically significant differences in the other clinical parameters, such as age, hemoglobin level, WBC and platelet counts, between the CD34+ and CD34- groups. There were no differences between the two groups in terms of complete remission, overall survival and disease-free survival (*data not shown*). A comparison between the two groups excluding the M_{3v} cases confirmed the previous results, except for the difference in HLA-DR expression. Analysis of the clinical significance of CD2 expression in the entire group of 136 patients did not yield evidence of any difference in terms of overall and disease-free survival between the CD2+ patients (n=33) and the CD2- patients (n=103).

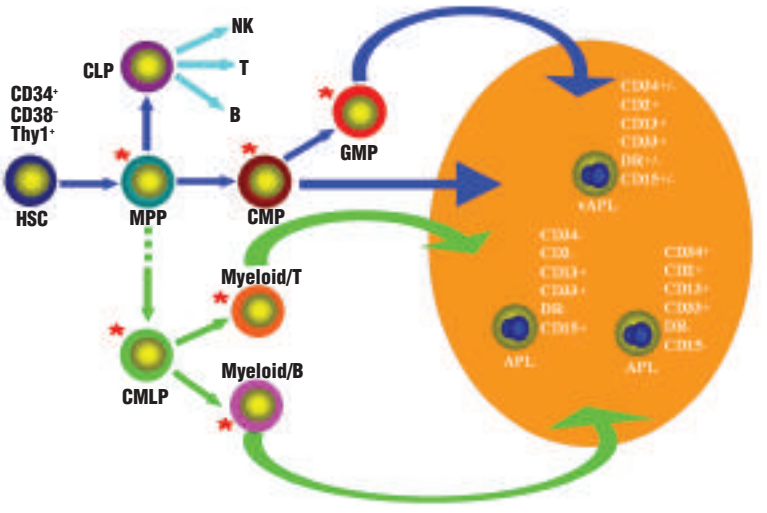

Figure 2. Hypothetical model for the pathogenesis of different subsets of APL. Considering the accepted model for the hematopoietic differentiation pathways, CD34⁺CD2⁺ APL may arise from the MPP, prior to lineage commitment, or from myeloid committed cells (CMP, GMP); in the CMP and GMP the aberrant expression of lymphoid markers may be a consequence of lineage-affiliated gene deregulation occurring during the process of leukemic transformation. As an alternative, a conceivable explanation for the origin of CD34⁺CD2⁺ APL is the *lineage promiscuity model*: APL may start from the CMLP or progenitor populations (Myeloid/T and Myeloid/B), with myeloid and lymphoid differentiation potential, undergoing leukemic transformation. Potential points at which PML-RARα could arise leading to induction of the APL phenotype are indicated by a red asterisk.

HSC: hematopoietic stem cell; MPP: multipotent progenitor; CLP: common lymphoid progenitor; CMP: common myeloid progenitor; CMLP: common myeloid and lymphoid progenitor; GMP: granulocyte/monocyte restricted progenitor; APL: acute promyelocytic leukemia; vAPL: variant acute promyelocytic leukemia.

CD34⁺CD2⁺ vs CD34⁻CD2⁻

Among the 136 APL cases, 24 (17.6%) and 80 (58.8%) were identified as CD34⁺CD2⁺ and CD34⁻CD2⁻, respectively (Figure 1). The two groups showed differences in terms of M3v frequency (6 [25%] vs 0 [0%]; $p<0.0001$), WBC count (9.9×10^9/L vs 1.8×10^9/L; $p=0.0004$), platelet count (21×10^9/L vs 28×10^9/L; $p=0.03$) percentage of peripheral blood leukemic promyelocytes (88% vs 28%, $p=0.0001$), and bcr3 expression (15 [68%] vs 14 [24.5%], $p=0.0006$) (Table 2).

There were no differences between the two groups in terms of complete remission, overall survival and disease-free survival (*data not shown*). After excluding the M3v patients from the analysis the CD34⁺CD2⁺ group showed higher WBC counts (8.2×10^9/L vs 1.8×10^9/L, $p=0.004$), lower platelet counts (22×10^9/L vs 28×10^9/L, $p=0.04$), a higher percentage of peripheral blood leukemic promyelocytes (87% vs 28%; $p=0.002$), and was associated with bcr3 expression (12 [75%] vs 14 [24.6%]; $p=0.0006$). Moreover, the proportion of CD15⁻ cases was higher in the CD34⁺CD2⁺ group (15 [93.7%] vs 37 [68.5%]; $p=0.05$). Analysis of the data showed that there were no differences between the two groups in terms of complete remission, overall survival and disease-free survival. When we compared the CD34⁺CD2⁺ group with the 20 CD34⁺CD2⁻ patients, significant differences persisted between the two groups in terms of WBC count, percentage of peripheral blood leukemic promyelocytes and CD15 expression.

CD34⁺CD2⁺ vs M3v

In our APL series there were 18 cases of M3 CD34⁺CD2⁺ (13.2%) and 12 cases of M3v (8.8%) (Table 3). Compared to the M3v cases the CD34⁺CD2⁺ group showed a higher proportion of CD34⁺ cases ($p=0.01$), and lower proportions of CD15⁺ and HLA-DR⁺ cases ($p=0.001$ and $p=0.03$, respectively). Moreover, the proportion of cases with the bcr3 isoform was higher in the CD34⁺CD2⁺ group than in the M3v group (12 [75%] vs 3 [30%]; $p=0.04$). There were no statistically significant differences between the two groups in terms of complete remission, overall survival and disease-free survival (*data not shown*), although the median disease-free survival in the M3v group was 29 months whereas it was not reached in the other group ($p=0.2$). Moreover, further analysis of disease-free survival revealed that patients with M3v had a higher probability of relapse than had M3 cases included in this study ($p=0.02$).

Discussion

The focus of this study was to analyze CD34 expression in adult APL. In previous reports this kind of analysis was compromised by various forms of bias such as a very low number of analyzed cases, failure to distinguish M3 from M3v cases, and a mixture of adult and pediatric APL patients.[9,11-13]

Given the differentiation level of promyelocytes, one would expect the progenitor antigen CD34 to have been lost in APL. In fact, low or negative CD34 expression in addition to absent HLA-DR used to be the paradigm of the APL immunophenotype. However, the frequency of CD34⁺ expression in APL has been found to range from 20 to 31% in different studies.[9-13] Our report confirmed these values, showing a frequency of 34.5%. The significance of CD34 expression is unknown but it likely identifies an immature form of APL. The first point of interest in our results is the strong association between CD34 and

CD2 expression. The co-expression of these two surface antigens was still evident even when the M3v cases were excluded from the analysis; this fact reveals the existence of a subgroup of APL with biological characteristics similar to those of the M3v (percentage of peripheral blood leukemic promyelocytes, WBC, and platelet counts, association with bcr3 expression) but substantially different in terms of expression of cell-surface antigens (higher CD34 and lower CD15 expression in the CD34+CD2+ group). The frequency of this subgroup was 14.5% (excluding the M3v cases). The mechanism leading to aberrant expression of lymphoid markers in acute myeloid leukemia still remains obscure. According to the *lineage infidelity* model,[19] this phenomenon is a consequence of deregulation of lineage-affiliated genes occurring during the process of leukemic transformation, whereas, according to the *lineage promiscuity* model,[20] co-expression of myeloid and lymphoid markers reflects the immunophenotype of the progenitor population subject to leukemic transformation, which is then perpetuated in the leukemic progeny.

Recent studies that have considered the gene expression profiles of highly selected murine bone marrow progenitor populations suggest that myeloid and lymphoid genes are co-expressed in multipotent progenitors prior to lineage commitment.[21-22] The process of myeloid commitment is correlated with progressive silencing of lymphoid and natural killer (NK) affiliated genes such that only myeloid and erythroid genes are expressed in common myeloid progenitors. Conversely, lymphoid commitment is associated with a progressive silencing of myeloid genes, such that only B-, T- and NK-lineage-affiliated genes are expressed in common lymphoid progenitors. If this widely accepted model of hematopoietic lineage commitment and differentiation is indeed correct, the *lineage promiscuity* model would imply that some cases of APL arise in progenitors that have not undergone lineage restriction.

Therefore, high CD34 expression together with low CD15 expression could suggest a distinct APL leukemic cell fraction characterized by poor differentiation, recognizable via contemporary CD2 analysis (Figure 2).

It has been reported that the expression of CD56 is significantly associated with a shorter duration of complete remission and inferior survival in patients with APL treated with all trans retinoic acid plus chemotherapy.[23] Our analysis showed that there was not a different distribution of CD56 expression between the CD34+CD2+ and CD34-CD2- groups. In terms of overall survival and disease-free survival there were no differences among the groups compared. Lee *et al.*[11] reported that CD34+ APL was associated with short overall and disease-free survival, but these data do not seem to be very informative because of the low number of cases (10 CD34+ patients) and the lack of information about the number of M3v patients analyzed. Their data may be misleading due to a high proportion of M3v cases in the CD34+ group. In this respect, our analysis of disease-free survival revealed that patients with M3v had a higher probability of relapse than did those with M3. These data further stress the importance of distinguishing the classic M3 subtype from the hypogranular variant cases in this kind of analysis.

We did not evaluate internal tandem duplications of the *FLT3* gene in this study. It was recently reported that *FLT3* internal tandem duplications were associated with high WBC count, M3v subtype and the bcr-3 PML-RARα isoform in a large series of APL patients.[24] Hence, it is possible that further studies on CD34+CD2+ APL subtype will clarify whether this kind of APL is different from the classic and variant types in terms of *FLT3* gene mutations and genomic expression profiles.

Our findings suggest that immunophenotypic analysis could distinguish an APL subset with different biological characteristics. Further studies in APL patients are needed to assess whether a heterogeneous immunophenotypic pattern could have a prognostic impact.

FA and GS contributed to the concept and design of the manuscript. FA supplied statistical expertise, interpreted and analyzed the data, and wrote the manuscript. AM, AP, DP, FL, BM, FF, FN and PC collected and assembled the data. GS, VL, and GC gave final approval. The authors declare that they have no potential conflicts of interest.

Manuscript received August 19, 2005, Accepted December 21, 2005.

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