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Is Flow Cytometric Immunophenotyping Useful for Predicting Acute Myeloid Leukemia Prognosis?

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Abstract

Introduction: Acute myeloid leukemia (AML) is an aggressive clonal myeloid neoplasm that causes the accumulation of myeloblasts in blood and bone marrow. This study aimed to determine immunophenotypic characteristics and their prognostic value in patients with AML, to compare the results of patients with the literature and to reveal regional differences.

Methods: Data of 100 patients (aged <65 years) who were diagnosed as having acute leukemia based on the World Health Organization diagnostic criteria (2008) and who underwent 7+3 remission induction chemotherapy in Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Hematology division n 2008–2015. The immunophenotype of bone marrow samples from the patients were analyzed using flow cytometry.

Results: Fifty-two patients (52%) were males and 48 (48%) were females; the mean age at diagnosis was 49±11.4 (18-62) years. The overall survival was 203.0±74.6 (0-1666) days, and the disease-free survival time was 137.0±46.7 (0-1588) days. Considering the response to induction therapy, complete response was 53% (n=53), non-response was 16% (n=16), and death during the induction was 31% (n=31). At the time of statistical analyses, 35% (n=35) of patients were in remission and 65% (n=65) were dead. There was no difference between CD56 positive and negative group regarding CD34 and CD7 positivitiy, cytogenetic risk groups, complete remission, disease-free and overall survival time. The pan-myeloid markers (CD13, CD33, CD15, and MPO) also had no effect on survival. Aberrant markers (CD19, CD7, and CD2) did not have any effect on prognosis. Tdt coexpression is the only poor prognostic antigen that is effective on survival.

Conclusion: In AML prognosis, there is no effect of the antigens alone. We think that patients should be evaluated together with immunophenotypic, cytogenetic and other prognostic factors.

Keywords: Acute myeloid leukemia, immunophenotype, prognostic antigen

Introduction

Acute myeloid leukemia (AML) is an aggressive clonal myeloid neoplasia that causes accumulation of myeloblast in the blood or bone marrow. For diagnosing AML, at least 20% of nucleated cells in the blood or bone marrow are required to include myeloblasts according to the current classification of the World Health Organization (WHO). This threshold value is 30% according to the French-American-British (FAB) classification system (1).

Flow cytometry with multiple parameters is used for determining the relationship of the origin in newly diagnosed acute leukemia (2-4). For diagnosing AML, particularly CD3, CD7, CD13, CD14, CD33, CD34, CD64, and CD117, cytoplasmic myeloperoxidase (MPO) and human leukocyte antigen D-related (HLA-DR) should definitely be evaluated while performing immunophenotypic studies. In lymphoid cells such as cCD3 and cCD79a, the absence of specific surface markers should be demonstrated. In order to determine the rate of blasts in immunophenotypic studies, CD45, CD34, or CD117 should be used (5).

Variables used to aid the prediction of the course of disease and response to treatment beforehand are called prognostic factors. These prognostic factors can be divided into two groups as those related to the general health state of the patient and those related to the biological features of leukemia. Patients with advanced age (>60 years), poor performance, comorbid diseases, secondary AML, presence of dysplasia, absence of Auer rods, sub-types of M0, M5, M6, and M7, CD34 expression, CD56 expression, presence of extramedullary disease, presence of fibrosis in the bone marrow, slow response to cytoreduction, more than one chemotherapy applied for obtaining full response, presence of Philadelphia chromosome, monosomies in the 5th and 7th chromosomes, complex karyotypes, and presence of FMS-like tyrosine kinase 3 (FLT3) are associated with poor prognosis. On the other hand, the presence of Auer rods, M3 and M4Eo sub-types according to the FAB classification, presence of t(8;21), t(15;17), inversion (inv) 16, and t(16;16), and presence of nucleophosmin-1 (NPM1) and CCAAT/enhancer binding protein alpha are associated with good prognosis (6, 7).

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The aims of our study are to determine the effects of flow cytometric immunophenotyping findings on the prognosis of patients diagnosed with AML, to compare our results with data in the literature, and to contribute to the literature.

Material and Methods

In the present study, 111 patients who were younger than 65 years old and diagnosed with AML according to the WHO 2008 diagnosis criteria of acute leukemia in the Division of Hematology under the Department of Internal Medicine at Eskişehir Osmangazi University between the years of 2008 and 2015 were evaluated. Eleven AML patients were excluded from the study because they did not receive "7+3" remission induction chemotherapy.

Flow Cytometric Immunophenotyping and Laboratory Tests

Flow cytometric immunophenotyping was studied on bone marrow aspiration sample. The samples were stained to identify CD2, CD3, CD5, CD7, CD10, CD13, CD14, CD15, CD19, CD22, CD33, CD34, CD64, CD45, CD56, CD117, HLA-DR, MPO, and terminal deoxynucleotidyl transferase (Tdt) (Becton Dickinson, Mountain View, CA, USA) monoclonal antibodies. Positivity of a marker was defined as the presence of the marker presented by a cell at 20% and above level. Complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), biochemical tests, karyotype analysis, FLT3, NPM1, t(15;17), t(8;21), and inv(16) results were evaluated as laboratory parameters.

Statistical Analysis

For the statistical analysis of the obtained data, Statistical Package for Social Science (SPSS) 22.0 for Windows (IBM Corp.; Armonk, NY, USA) software was used. A p value of <0.05 was accepted as statistically significant. Chi-square test was employed for evaluating the crosstabs. Life curve graphs were drawn by using the Kaplan-Meier analysis for comparing lifetimes between the groups. The log-rank test was used for revealing the differences between the groups. In the identification of prognostic variables affecting lifetime, the stepwise Cox regression technique was used.

Data were presented as mean±standard deviation and number-%. The ethical approval for the study was obtained from the ethics committee of Eskişehir Osmangazi University Medical Faculty (decision date: 12.15.2014 and no. 80558721/312).

Table 1. Laboratory findings of 100 cases with AML

Laboratory parameters	Mean±standard deviation (min–max)
Hemoglobin (g/dL)	9.2±2.1 (2.5-14)
Leukocyte (/mm3)	39.820±(300-289,000)
Platelet (/mm3)	64,616±84,626 (3600-631,000)
Potassium (mEq/L)	4.1±0.5 (2.79-5.61)
Lactate dehydrogenase (U/L)	1291 (68-6430)
Uric acid (mg/dL)	5.80±2.30 (1.31-18.80)
Erythrocyte sedimentation rate (mm/h)	72.1±39.8 (5-157)
C-reactive protein (mg/dL)	6.5±8.0 (0.3-36.10)

AML: acute myeloid leukemia

Results

A total of 100 patients with AML, who were younger than 65 years old, diagnosed and classified according to the WHO 2008 diagnostic criteria, and given classical remission induction chemotherapy, were retrospectively evaluated.

Of all cases, 52 (52%) were males, and 48 (48%) were females. The mean age of the patients at the time of diagnosis was 49±11.4 (18-62) years. The number of patients with Eastern Cooperative Oncology Group performance score of ≤1 was 95 (95%).

At the time of admission, the mean hemoglobin value of the patients was 9.2±2.1 g/dL (2.5-14), the mean white blood cell count was 39,820±54,505/mm^3 (300–289,000), and the mean platelet count was 64,616±84,626/mm^3 (3600-631,000). Biochemical parameters, ESR value, and CRP values at the time of admission are shown in Table 1.

In the classification of cases with the diagnosis of AML according to the WHO 2008 classification, 26 patients were included in the AML group accompanied by recurrent genetic anomalies. Among them, t(8;21) (+) was detected in 3, inv(16) (+) in 6, and t(15;17) (+) in 17. Sixty-three of the patients were included in the AML group not otherwise classified. Of these patients, 12 were in the minimal differentiation group, 15 were in the immature group, 14 were in the granulocytic maturity displaying AML group, 16 were in the acute myelomonocytic leukemia group, and 5 were in the acute monoblastic/monocytic leukemia group. Of the patients, 3 were included in the AML group with myelodysplasia-related changes, 3 were in the treatment-related myeloid neoplasia group, 2 were in the AML group with panmyelosis and myelofibrosis, 1 was in the mixed phenotype acute leukemia t(9;22)(q34;q11.2)BCR-ABL group, and 3 were in the mixed phenotype acute leukemia t(v;11q23)MLL group.

Primary AML was found in 92 of the patients, and secondary AML was found in 8 of the patients. Of 8 secondary AML cases, 3 were myelodysplastic syndrome, 2 were myelofibrosis, 1 was Hodgkin's lymphoma, 1 was anaplastic lymphoma, and 1 was AML developing after testicular carcinoma.

In the cytogenetic examination, karyotype analyses of 57 patients were achieved. Of 57 patients, 36 displayed normal karyotype (46 XX or 46 XY), and 21 displayed abnormal karyotype.

When the patients were classified with respect to cytogenetics and molecular genetics, detailed genetic information was not achieved in 4 out of 100 patients. Of 96 patients, 35 were in good cytogenetic risk group, 47 were in moderate cytogenetic risk group, and 14 were in poor cytogenetic risk group.

The mean total survival of the patients was 203.0±74.6 (0-1666) days, and disease-free survival was 137.0±46.7 (0-1588) days. The rates of responses to the induction chemotherapy were as follows: 53% full response (n=53), 16% no response (n=16), and 31% mortality during induction (n=31). Recurrence occurred in 15% (28%) of the patients giving full response to induction chemotherapy. According to the last evaluation of the patients' states, 35% (n=35) were in remission, and 65% (n=65) died. When the mortality

Table 2. CD34, CD7, karyotype, cytogenetic, and complete remission differences in patients with CD56(+) and CD56(-)

	CD56(+)	CD56(-)	p
CD34	13/26	33/74	>0.05
CD7	6/26	17/74	>0.05
Normal karyotype	11/17	24/40	>0.05
Poor cytogenetic risk	4/25	10/71	>0.05
Moderate cytogenetic risk	14/25	33/71	>0.05
Good cytogenetic risk	7/25	28/71	>0.05
Complete remission	16/26	37/74	>0.05

Table 3. The frequency of surface markers evaluated in patients with AML classification according to the FAB classification system

	AML M0	AML M1	AML M2	AML M3	AML M4	AML M5	AML M6
CD34	10/14	13/18	9/21	4/17	9/24	0/5	1/1
CD10	0/14	0/18	0/21	0/17	1/24	0/5	0/1
CD2	0/14	0/18	0/21	1/17	0/24	0/5	0/1
CD19	2/14	1/18	3/21	3/17	0/24	0/5	0/1
CD14	1/14	1/17	3/21	1/17	16/24	4/5	0/1
CD13	9/14	15/17	17/21	17/17	22/24	3/5	1/1
CD33	12/14	17/17	21/21	17/17	24/24	4/5	1/1
HLA-DR	10/14	8/17	17/21	1/17	17/24	5/5	1/1
CD7	6/14	8/18	5/21	1/17	2/24	1/5	0/1
CD117	8/12	7/16	9/21	7/16	12/23	0/5	0/1
CD64	5/14	9/17	13/21	12/17	22/24	4/5	1/1
CD15	4/14	9/17	10/21	9/17	20/24	4/5	1/1
CD56	3/14	5/18	7/21	0/17	9/24	2/5	0/1
MPO	3/14	16/17	18/21	15/17	9/24	3/5	1/1
CD3	0/14	0/17	0/21	0/17	0/24	0/5	0/1
Tdt	2/14	2/18	0/21	0/17	0/24	0/5	0/1
CD22	2/14	2/17	1/21	0/17	0/24	0/5	1/1
CD5	2/14	0/18	0/1	0/17	0/24	0/5	0/1

FAB: French-American-British; AML: acute myeloid leukemia; MPO: myeloperoxidase; Tdt: terminal deoxynucleotidyl transferase

causes of exitus patients were examined, the most common causes were found to be fungal pneumonia in 10 (15%) patients, fungal pneumonia + sepsis in 22 (33.84%) patients, and cerebrovascular event in 13 (20%) patients.

No significant difference was detected in the patient groups with and without CD56(+) in terms of CD34, CD7, karyotype, cytogenetic classification, and complete remission (p>0.05). These features of the patients are presented in Table 2.

Whereas the mean total survival length was 381±143 days in patients with CD56(+), it was 182±46.2 days in patients with CD56(-). There was no statistically significant difference (p>0.05).

Of the patients, 46% (n=46) had CD34(+), 26% (n=26) had CD56(+), 23% (n=23) had CD7(+), 1% (n=1) had CD2(+), 9% (n=9) had CD19(+), and 4% (n=4) had Tdt (+). In 43% (n=43) of the patients, panmyeloid markers (CD13, CD33, MPO, and CD15) were found as positive. CD13 was found as positive in 84% (n=84), CD33 in 96% (n=96), MPO in 75% (n=75), CD15 in 57% (n=57), HLA-DR in 59% (n=59), CD14 in 26% (n=26), CD64 in 66% (n=66), CD5 in 2% (n=2), CD22 in 6% (n=6), CD10 in 1% (n=1), and CD117 in 43% (n=43).

Table 4. Molecular analysis, karyotype, and cytogenetic relationship according to the FAB classification

	AML M0	AML M1	AML M2	AML M3	AML M4	AML M5	AML M6
Normal karyotype	3/6	8/12	8/12	5/11	8/12	2/3	1/1
Abnormal karyotype	3/6	4/12	4/12	6/11	4/12	1/3	0/1
t(8;21)	0/4	0/10	2/16	–	0/11	0/1	–
t(15;17)	0/2	0/3	0/8	16/17	0/5	–	–
inv(16)	0/3	0/4	8/11	–	4/16	0/1	–
Trisomy 8	2/6	0/12	0/12	0/11	0/12	0/3	0/1
5/7 abnormality	1/6	2/12	2/12	0/11	1/12	1/3	1/1
Good cytogenetic risk	2/13	2/16	7/21	15/17	7/24	2/4	0/1
Moderate cytogenetic risk	7/13	9/16	13/21	13/21	1/17	15/24	1/4
Poor cytogenetic risk	4/13	5/16	1/21	1/17	2/24	1/4	0/1

FAB: French-American-British; AML: acute myeloid leukemia; inv: inversion

In the comparison of CD7 and cytogenetic risk, no statistically significant difference was detected between the groups with CD7(+) and (-) and poor, moderate, and good risk groups (p>0.05).

Whereas the mean total survival length was 232±100 days in patients with the panmyeloid markers (CD13, CD33, CD15, and MPO), it was 200±126.7 days in patients without these markers. No statistically significant difference was found between the two groups in terms of the total survival length (p>0.05). The mean disease-free survival length was 180±64.1 days in patients with the panmyeloid markers, and it was 128±89.3 days in those without the panmyeloid markers. There was no statistically significant difference between the two groups with regard to disease-free survival (p>0.05).

Moreover, no significant difference was seen between the groups with and without the aberrant marker of CD19(+) in terms of the total survival and disease-free survival (p>0.05).

In patients with the aberrant marker of Tdt (-), the mean length of disease-free survival was 574.975±77.4 days. The mean length of disease-free survival was 188±11.8 days in 4 patients with Tdt (+), and all of these 4 patients were exitus. However, there was no statistically significant difference (p>0.05). With regard to the total survival length, the mean total survival was 624.466±77.9 days in patients with Tdt (-) and 255.250±131.4 days in patients with Tdt (+), and the difference was not statistically significant (p=0.790).

The aberrant marker of CD2 was observed as (+) only in one patient, and the total survival time of the patient was 17 days.

When our patients with AML were classified according to the FAB classification system, 14% (n=14) were AML M0, 18% (n=18) were

AML M1, 21% (n=21) were AML M2, 17% (n=17) were AML M3, 24% (n=24) were AML M4, 5% (n=5) were AML M5, and 1% (n=1) were AML M6. Surface marker features of the patients with AML according to the FAB classification are shown in Table 3.

The relationships of the groups with molecular analysis, karyotype, and cytogenetics according to the FAB classification are presented in Table 4.

Discussion

Flow cytometry with multiple parameters is used for determining the origin relationship in newly diagnosed acute leukemia (2-4). In order to find the rate of blasts, CD45, CD34, or CD117 is used in immunophenotypic studies (5). The presence of CD56 antigen in blast cells affects the process of complete remission and survival. In acute promyelocytic leukemia, the presence of CD56 in blasts is considered as poor prognostic risk group (8). In various studies, undesired immunophenotypic markers that cause predictive poor results include CD7, CD19, CD11b, CD13, CD14, CD33, CD34, CD56, and Tdt. The coexistence of CD34 and HLA-DR is the independent predictor marker for unsuccessful complete remission (9). In the study by Raspadori et al. (8), CD56(+) was reported in 24% of the patients. Whereas full response was obtained in 12 (36%) out of 33 patients with CD56(+), it was obtained in 59 (68%) out of 87 patients with CD56(-). No apparent relationship was found between CD56 and CD34 and CD7 expression. However, there was a clear relationship between CD56 expression and poor cytogenetic risk. Moreover, CD56(+) was evaluated to be an independent prognostic factor for full response. In our study, CD56(+) was found in 26% of the patients. Whereas full response was obtained in 16 (61.5%) out of 26 patients with CD56(+), full response was achieved in 37 (50%) out of 74 patients with CD56(-).No significant difference was observed between the groups with and without CD56(+) and CD34, CD7, karyotype, cytogenetic classification, and complete remission. The total survival length of patients with CD56(+) was higher than that of patients with CD56(-). Different from other studies, CD56 positivity was not found to be an effective factor for survival in our study. On the contrary, despite no statistically significant difference, the patients with CD56(+) were revealed to survive longer.

In the study by Tong et al. (10), they reported CD13(+) in 96.4% (185/192) of the patients, CD33(+) in 91.7% (176/192), MPO(+) in 83.9% (161/192), CD34(+) in 65.1%, HLA-DR(+) in 77.6%, CD56(+) in 26%, CD7(+) in 20.8%, CD19(+) in 9.9%, and CD2(+) in 7.3%. Negative MPO was found in all AML M0 and M7 patients. CD34(+) and HLA-DR(+) were detected to be lower in the subgroup of AML M3. CD56(+) was more common in AML M1 and AML M5 subgroups. t(8;21) (+) was found in 17 AML M2 patients, t(15;17) (+) in 28 AML M3 patients, and inv(16) (+) in 2 AML M4 patients. In the study by Webber et al. (9), 91% CD13(+), 87% CD33(+), 80% CD117(+), 71% CD34(+), 79% HLA-DR(+), 16% CD14(+), 28% CD7(+), 18% CD2(+), 13% CD10, and 8% CD19(+) were reported. Of the patients in our study, 46% (n=46) had CD34(+), 26% (n=26) had CD56(+), 23% (n=23) had CD7(+), 1% (n=1) had CD2(+), 9% (n=9) had CD19(+), and 4% (n=4) had Tdt (+). Panmyeloid markers (CD13, CD33, MPO, and CD15) were found to be positive in 43% (n=43). CD13 was detected as positive in 84% (n=84), CD33 in 96% (n=96), MPO in 75% (n=75), CD15 in 57% (n=57), HLA-DR in 59% (n=59), CD14 in 26% (n=26), CD64 in 66% (n=66), CD5 in 2% (n=2), CD22 in 6% (n=6), CD10 in 1% (n=1), and CD117 in 43% (n=43). In our study, MPO positivity (3/14) was determined at the lowest rate in the AML M0 subgroup. HLA-DR(+) (1/17) was the lowest in the AML M3 subgroup. Whereas CD56(+) was higher in the AML M5 subgroup, it was not found in the subgroups of AML M3 and AML M6.

In the study conducted by Legrand et al. (11), four of the panmyeloid markers (MPO, CD13, CD33, CDw65, and CD117) were positive in 36% of the patients and five markers were positive in 28% of the patients, and complete remission rate was detected to be higher in the group with positive panmyeloid markers. Whereas the rate of disease-free survival was reported to be 52% in panmyeloid positive patients, it was 16% in panmyeloid negative patients. In the panmyeloid positive patients, the total survival rate was found as 48%, and the median total survival time was 780 days. However, in panmyeloid negative patients, the total survival rate was 17%, and the median total survival time was 190 days. In 43% of our patients, panmyeloid markers (CD13, CD33, CD15, and MPO) were positive. Whereas the mean total survival length was 232±100 days in patients with positive panmyeloid markers, it was 200±126.7 days in patients without panmyeloid markers. There was no statistically significant difference between the two groups in terms of the total survival length. The mean disease-free survival length was 180±64.1 days in patients with panmyeloid markers and 128±89.3 days in patients without panmyeloid markers. Different from the literature, the effect of positive panmyeloid markers on disease-free and total survival was not revealed, and this result suggests the presence of different factors influencing total survival.

Several studies have demonstrated that lymphoid antigens expressed from myeloblasts affect the prognosis poorly, well, or ineffectively in AML. The most commonly detected lymphoid markers in AML are CD56 and CD7 (11). In the study by Cross et al. (12), the coexpression of CD2, CD3, and CD7 with myeloid antigens was demonstrated to be associated with poor prognosis. However, in other studies, CD7 could not be demonstrated as a prognostic marker for AML (10). In some other studies, the coexpression of lymphoid antigens such as CD2 and CD19 was reported to be related to good prognosis (13, 14). In our study, the most common lymphoid antigens displaying coexpression were CD19 and CD7, but the effects of CD19 and CD7 coexpression on AML prognosis could not be demonstrated as in some studies in the literature (10).

The effect of Tdt positivity on prognosis is not clear. Casasnovas et al. (15) found Tdt positivity to be associated with chromosomal abnormalities. On the other hand, Legrand et al. (11) reported no relationship between Tdt positivity and chromosomal abnormalities. In the study by Zheng et al. (16), a relationship was shown between CD22, CD56, and Tdt expression and abnormal chromosomal karyotype. The mean length of disease-free survival was 574.975±77.4 days in patients with the aberrant marker of Tdt (-) and 188±11.8 days in four patients with Tdt (+), and these four patients were exitus. However, no statistically significant difference was found.

With regard to the total survival length, the mean total survival was 624.466±77.9 days in patients with Tdt (-) and 255.250±131.4 days in those with Tdt (+), and the difference was not statistically significant. Although the number of patients with Tdt (+) was low, Tdt positivity seems to be associated with poor prognosis in AML patients.

Conclusion

The effect of CD56 coexpression on CD34, CD7, karyotype, cytogenetic classification, complete remission, and disease-free and total survival was not determined. Different from the studies, the effect of panmyeloid markers (CD13, CD33, CD15, and MPO) on survival could not be found. Moreover, the effect of the presence of the aberrant markers of CD19, CD7, and CD2 was also not revealed. Tdt coexpression is the only poor prognostic antigen that has an effect on survival. We suggest that antigens on the surface of blasts do not affect AML prognosis alone, and patients should be evaluated together with immunophenotypic, cytogenetic, and other prognostic factors.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee.

Informed Consent: Informed consent is not necessary due to the retrospective nature of the study.

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