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Significance of CD34-Positive Cells in Children with B-Cell Acute Lymphoblastic Leukemia: A Case-Control Study

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common cancer among children. The prognostic significance of the cluster of differentiation 34 (CD34) markers in children with B-cell acute lymphoblastic leukemia (B-ALL) is not yet fully understood.

Materials and Methods: This study is a case-control trial based on the clinical data of 40 children with B-ALL who referred to a pediatric oncology center in the city of Sari, Iran. The data were derived from the demographic findings, laboratory test results at diagnosis, immunophenotyping, transfusion of blood products including packed red blood cells and platelet concentrates, and the frequency and duration of hospitalization due to febrile infection.

Results: Of the participants, 42.5% were CD34-negative and 57.5% were CD34-positive. The mean age of the patients at diagnosis was 3.1 ± 3.3 years (Range:0.1-13.3 years). Also, 60.9% of the CD34-positive children and 47.1% of the CD34-negative ones were boys (P = 0.38). According to the calculated Cohen's d, the relationship of CD34 positivity with transfused packed red blood cell and platelet concentrates was mild -0.15 (95% CI -0.78 to 0.47) (P = 0.55) and moderate 0.49 (95% CI -0.15 to 1.12) (P = 0.29), respectively, which was significant in neither case. Moreover, the relationship of CD34 positivity with the hospitalization frequency of -0.51 (95% CI -1.14 to 0.13) (P = 0.22) and the hospitalization duration of -0.52 (95% CI -1.16 to 0.12) (P = 0.27) due to febrile infection was moderate to strong.

Conclusion: The CD34-positive children with B-ALL experienced less blood products transfusion (except packed red blood cells) and febrile infection in terms of both the frequency and duration of hospitalization during chemotherapy. Therefore, CD34 expression in the B-ALL children was associated with better prognosis.

Keywords: Child, Precursor cell lymphoblastic leukemia-Lymphoma, Prognosis

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer among children; it accounts for over 80% of all acute leukemia cases (1, 2). It can be classified into B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL). Of ALL cases, 85% are B-ALL, and 15% are T-ALL (3, 4). Fever, petechiae, ecchymosis, gum bleeding, bone pain and distributed lymphadenopathy as well as central nervous system symptoms such as headache, vomiting and paralysis are the main symptoms of ALL (3, 5).

Cell immunophenotyping by flow cytometry not only determines the origin, type and blasts maturation stage but also helps to decide on a diagnostic and therapeutic approach for patients (6, 7). In addition to its role in diagnosis and prognosis, immunophenotyping by flow cytometry also helps to assess the course of the disease (8-11). Chemotherapy is done through risk classification based on clinical features (e.g., 1–9.9 years of age vs. <1 or ≥10 years) and white blood cell (WBC) counts at diagnosis (<50 × 109/L vs. ≥50 × 109/L), cytogenetic and genomic study of ALL cells, and response

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assessment with a minimal residual disease (MRD) assay (12). The cell-surface marker, CD34, was first identified as a hematopoietic cell-surface antigen (13), and the presence of CD34-positive cells in flow cytometry was noted as a good prognostic marker of patients with B-ALL (14-16). In addition to the CD34 marker, there are CD20, CD22, CD10 and CD19 regarded as the other specific markers for B-ALL (6). The aim of our study is to determine the significance of CD34 expression in children with acute lymphoblastic leukemia and its correlation with treatment complications and consumption of blood products.

Materials and Methods

This is a case-control study conducted on standard-risk B-ALL patients aged from 2 months to 18 years admitted to the Pediatric Hematology and Cancer Center of Bu Ali Sina Hospital in the city of Sari from the first of 2010 to the end of 2021. Following a study by Pui et al. (17), the STATA-15 software was used to calculate the sample size. The calculation was based on the comparison of the average hemoglobin concentrations in the case and control groups (i.e., patients with B-cell ALL of positive and negative CD34 types). Considering SD1 = 1.8, SD2 = 1.8, M1 = 7.5, M2 = 9.0 (d = 1.5 gr/dl for the hemoglobin level), 23 people were assigned to each group (α = 0.05 and power = 0.80). Five patients in the CD34-negative group were excluded from the study due to incomplete file information. The inclusion criteria for this study were 2 months to 18 years of age, B cells acute lymphoblastic leukemia, absence of leukemia secondary to drugs and radiation, and consent to participate in the study. The patients were categorized into a CD34-positive group (case group) and a CD34-negative group (control group) based on CD34 expression determined through the flow cytometry of the first bone marrow aspiration at the time of diagnosis. The data were extracted by reviewing the patients' records. The demographic data (such as age and gender), the laboratory test results at the time of diagnosis, such as white blood cell (WBC) and neutrophil counts, platelet (Plt) count and hemoglobin (Hb) level, the immunophenotyping of the first bone marrow aspiration sample (Human leukocyte antigen-DR (HLA-DR), CD10, CD19, CD20 and CD22), the mean frequency and days of hospitalization due to febrile infection, mean G-CSF, mean PRBC, and mean platelet concentrate transfusion were extracted from the patients' records. The laboratory data taken into consideration were related to the first test during the hospitalization of the patients. Fever was measured with a thermometer. In this regard, a single recording of the oral temperature at 38.3°C or above and a recording of 38°C lasting for at least an hour were considered as fever (18).

Statistical analysis

The data were depicted using means and standard deviations. The normality of the quantitative data was checked by histograms and the Shapiro-Wilk test. To compare the numerical data for the CD34-positive and CD34-negative cases, the Mann-Whitney U test was performed in addition to a chi-square test for the qualitative data. To investigate the strength of the association between the rate of blood products transfusion and the frequency and days of hospitalization on one hand and the CD34 positivity in the ALL cases, Cohen's d was estimated alongside 95% CI. All the data analyses were performed using the STATA software V.13.0 (Stata Corporation, College Station, Texas, USA). A P-value of < 0.05 was also considered as the threshold of significance.

Ethical Consideration

The ethics committee of Mazandaran University of Medical Sciences approved

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the study (approval ID: IR.MAZUMS.REC.1400.097).

Results

Out of 40 patients studied, 23 (57.5%) were CD34-positive and 17 (42.5%) were CD34-negative. The mean age of the patients at diagnosis was 3.1 ± 3.3 years (Range: 0.1-13.3 years). Of them, 55% were boys (22 people) and 45% were girls (18 people). Their age at the disease onset was 3.9 ± 3.7 years in the CD34-positive group and 2.1 ± 2.7 years in the CD34-negative group. The age difference of the two groups at the time of admission was not significant. Of the CD34-positive patients, 60.9% (n = 14) were boys and 39.1% (n = 9) were girls. Of the CD34– negative ones, there were 8 boys (47.1%) and 9 girls (52.9%). Basic characteristics of the participants are shown in Table I. In terms of gender, the CD34-positive and CD34-negative groups were not significantly different (P = 0.38). The level of HLADR was 25.6 ± 19.9 in the CD34-positive patients and 77.4 ± 25.5 in the CD34-negative ones. The difference of HLADR between the groups was significant. The CD10 level was 13.4 ± 20.4 in the CD34-positive patients and 75.8 ± 27.9 in the CD34-negative ones. The difference of CD10 between the two groups was significant. The CD19 level was 11.9 ± 22.3 and 74.8 ± 25.5 in the CD34-positive and CD34-negative patients, respectively. The difference of CD19 between the two groups was significant. The CD20 level was 4.03 ± 5.03 and 10.7 ± 10.9 in the CD34-positive and CD34-negative patients, and the difference was significant. Finally, the CD22 level was found to be 15.5 ± 26.6 and 37.4 ± 29 in the CD34-positive and CD34-negative patients, respectively. However, the difference between the two groups was not significant (Table II).

The mean white blood cell count in the CD34-positive patients was 4.41 ± 4.92. In the CD34-negative group, it was 3.96 ± 4.08. The mean absolute neutrophil count (ANC) was 216.1 ± 453.4 and 199.7 ± 372.9 for the CD34-positive and CD34-negative patients, respectively. The mean platelet count of the CD34-positive patients was 214.5 ± 189.5, and that of the CD34-negative group was 269.4 ± 174.2. The mean hemoglobin level in the CD34-positive and CD34-negative patients was 9.51 ± 2.43 and 9.93 ± 2.06, respectively. The two groups were not significantly different in terms of the mean hemoglobin level, the mean absolute neutrophil count and the mean platelet count (Table III). The mean rate of packed red blood cell (PRBC) transfusion was 1.13± 1.60 times for the CD34-positive patients and 1.46± 1.72 times for the CD34-negative ones, but the difference was not significant. Also, the number of PRBC transfusions for the CD34-positive patients was from 0 to 5 (median: 0), and it was the same for the CD34-negative patients but with median 1. Cohen's d level was found to be -0.20 (95% CI -0.83 to 0.43) and -0.15 (95% CI -0.78 to 0.47) for those groups, respectively. Concerning the frequency and volume of transfusion, there was a weak relationship between CD34 positivity and PRBC transfusion rate for the patients with B-ALL. The rate of platelet concentrate transfusion was 2.26 ± 4.60 times for the CD34-positive patients and 0.53 ± 1.12 times for the CD34-negative group. The difference in this case was not significant. Also, the frequency of platelet transfusion to the CD34-positive patients was from 0 to 17 (median: 0), but it was from 0 to 4 (median: 0) for the CD34-negative group. Also, Cohen's d levels were found to be 0.48 (95% CI -0.15 to 1.12) and 0.49 (95% CI -0.15 to 1.12) based on the frequency and volume of transfusion, indicating a moderate

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relationship between CD34 positivity and platelet transfusion rate for the patients with B-ALL. The mean frequency of fever in the CD34-positive patients was 1.26 ± 1.65, but it was 2.35 ± 2.66 times in the CD34-negative group. The difference in this case was not significant. The mean number of days of fever was 5.78 ± 8.59 for the CD34-positive patients and 12.1 ± 15.6 for the CD34-negative ones, but the difference was not significant between the two groups. In addition, Cohen's d levels were -0.51 (95%CI -1.14 to 0.13) and -0.52 (-1.16 to 0.12), indicating a moderate to strong relationship between the CD34 positivity of the B-ALL patients and the mean times and mean days of their hospitalization due to fever (Table **IV**) .

Table I: Basic characteristics of the cases

		CD34-positive (n = 23)	CD34-negative (n = 17)	P-value
Age at diagnosis		6.2 ± 4.1	5.2 ± 3.1	0.14
Gender	Male	14 (60.9%)	8 (47.1%)	0.38
	Female	9 (39.1%)	9 (52.9%)	

The results are presented as numbers and medians (interquartiles). The p-values were computed by the Mann-Whitney U-test and Chi-square test for the frequency data. CD: clusters of differentiation, G-CSF: granulocyte colony stimulating factor

Table II: The values of CD markers and HLA-DR levels for the CD34-positive and CD34-negative

	CD34-positive (n= 23)	CD34-negative (n=17)	MD (95% CI)	P-value
HLA-DR	25.6 ± 19.9	77.4 ± 25.5	-51.8 (-66.6 to -37.1)	**<0.0001**
CD10	13.4 ± 20.4	75.8 ± 27.9	-62.4 (-77.8 to -46.9)	**<0.0001**
CD19	11.9 ± 22.3	74.8 ± 25.5	-62.9 (-78.2 to -47.5)	**<0.0001**
CD20	4.03 ± 5.03	10.7 ± 10.9	-6.67 (-11.9 to -1.39)	**0.007**
CD22	15.5 ± 26.6	37.4 ±29	-21.9 (-48.8 to 5.06)	**0.05**

The data are presented as mean ± standard deviation or number (percentage). The p-values were computed by the Mann-Whitney U-test. MD: mean difference, CD: clusters of differentiation, HLA-DR: human leukocyte antigen-DR

Table III: The indices of CBC for the CD34-positive and CD34-negative cases

	CD34-positive (n = 23)	CD34-negative (n = 17)	MD (95% CI)	P-value
WBC level (10^9/L)	4.41 ± 4.92	3.96 ± 4.08	0.44 (-2.52 to 3.41)	0.71
ANC (10^9/L)	216.1 ± 453.4	199.7 ± 372.9	16.4 (-256.3 to 289.3)	0.43
Plt level (10^9/L)	214.5 ± 189.5	269.4 ± 174.2	-54.9 (-173.5 to 63.7)	0.27
Hb level (g/dl)	9.51 ± 2.43	9.93 ± 2.06	-0.41 (-1.89 to 1.06)	0.58

The data are presented as mean ± standard deviation or number (percentage). The p-values were computed by the Mann-Whitney U-test. CD: clusters of differentiation, CBC: complete blood count, MD: mean difference, WBC: white blood cell, ANC: absolute neutrophil count, Hb: hemoglobin, Plt: platelet

Table IV: The requirement of blood products transfusion for the CD34-positive and CD34-negative cases

	CD34-positive (n = 23)	CD34-negative (n = 17)	Cohen's d (95% CI)	P-value
Plt transfusion	2.26 ± 4.60	0.53 ± 1.12	0.48 (-0.15 to 1.12)	0.30
Plt transfusion (cc)	678.2 ± 1381.3	153.3 ± 335.6	0.49 (-0.15 to 1.12)	0.29
PRBC transfusion	1.13 ±1.60	1.46 ±1.72	-0.20 (-0.83 to 0.43)	0.42
PRBC transfusion (cc)	271.7 ± 386.4	333.3± 423.7	-0.15 (-0.78 to 0.47)	0.55
Mean times of fever	1.26 ± 1.65	2.35 ± 2.66	-0.51 (-1.14 to 0.13)	0.22
Mean days of fever	5.78 ± 8.59	12.1 ± 15.6	-0.52 (-1.16 to 0.12)	0.27

The data are presented as mean ± standard deviation or number (percentage). The p-values were computed by the Mann-Whitney U-test and Chi-square test. CD: clusters of differentiation, Plt: platelet concentrate, PRBC: packed red blood cells, Cohen's d: the value < 0.2 means weak, the range of 0.2 to 0.5 means moderate, and the range of 0.5 to 0.8 means large/strong, and > 0.8 means very strong.

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Discussion

This study focuses on the prognostic role of CD10 and CD34 in children with ALL and refers to their clinical relevance for the improvement of the prognosis and survival rate of children with B-ALL (19). The CD34-positive mode is reported as a favorable prognostic factor for pediatric B-ALL; it is associated with a reduced requirement for blood products during chemotherapy. The studied CD34-positive patients had fewer mean times and days of hospitalization due to febrile infection. To date, some association has been found between the CD markers of 20, 34, 44 and 95 and the clinical and laboratory conditions of ALL patients, but the findings are contradictory (19, 20).

The flow cytometry of the patients indicated that CD34-positive B-cells expressed fewer HLA-DR, CD10, CD19, CD20, and CD22 markers than in the control group. The difference was significant except for CD22. Also, CD34-positive patients with lower expression of the mentioned CD markers indicated less need for blood products (except platelets) and less febrile complications owing to chemotherapy. So, the presence of CD 34 marker was a good prognostic factor for the pediatric B-ALL.

Jeha et al. (20) and Mannelli et al. (21) found that increased CD20 expression was not associated with poorer prognosis and event-free survival (EFS). In a case-control study, Zahran et al. (22) investigated the role of CD146 in pediatric B-ALL and its relation with prognostic factors. The patients underwent immunophenotyping, and their CD markers of 10, 19, 22, and 34 were determined. The evaluation demonstrated a significant association of CD146 with CD34 positivity and bone marrow blasts. A significant negative correlation was also observed between the overall survival (OS) and disease-free survival (DFS) on one side and CD34 positivity on the other. It was concluded that CD34 positivity was a poor prognostic feature for pediatric B-ALL. In the present study, however, the CD 34 marker was shown to be a good prognostic factor for pediatric B-ALL. In the same context, Kamazani et al. (23) conducted a study to evaluate the expression of the CD markers of 95, 20, 34 and 44 as well as their prognostic significance in Iranian children with ALL. The assessment of CD20 with prognostic factors showed that this marker correlated to several poor prognostic ones, such as reduced Plt counts and involvement of organs other than bone marrow. The correlation was significant. Also, there was no significant relationship between CD markers and the duration of survival and complete remission.

Children suffer from immune suppression during chemotherapy, which is especially severe in the intensive induction phase. This makes them dependent on more support through blood products transfusion (24). The management of chemotherapy phases is very important because it is directly related to the destruction of leukemic cell colonies and their subsequent clinical prognosis. Therefore, the role of blood products in making the immune system of these patients strong enough to deal with the remaining colonies is undeniable. It should be noted that the immune suppression during the therapeutic process is proportional to the adverse effect of chemotherapy and blood products transfusion (25). The amount of blood products transfusion also helps to assess the disease status and the patients' treatment because it reflects the intensity of chemotherapy and the severity of the disease (26). The CD34-positive patients

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in this study consumed more Plt products during chemotherapy (approximately four times). This relationship between CD34 positivity and the need for platelets was moderate. It should be noted that CD34-positive patients had about 50,000 fewer platelets at admission. They also had less need for PRBC transfusions during chemotherapy. The correlation between PRBC transfusions and CD34 positivity was weak. Interestingly, the initial Hb level of the CD34-positive patients was lower than that of the opposite group. The evaluations showed a moderate to strong correlation between the number and duration of hospitalization due to febrile infection and CD34 positivity.

In a retrospective study, Dao Wang et al. (27) assessed the survival, prognosis, and recurrence rate of 163 children with ALL. Based on the number of transfusions, the study population was divided into four groups including without transfusion, 1 to 10 transfusions, 11 to 25 transfusions, and more than 25 transfusions. The results indicated that the decrease in survival rate was associated with the number of blood transfusions, and this relationship was strong (p-value < 0.01). Also, the number of transfusions was associated with poor prognosis. More than 25 transfusions were associated with the highest risk of poor prognosis (odds ratio = 3.97, p-value < 0.01). Transfusion more than 25 times was also associated with an increase in the recurrence rate (odds ratio = 4, p-value < 0.01). In the present study, however, there was no difference between the two groups in terms of the amount of PRBC transfusion, but the amount of platelet transfusion was higher in the CD34–positive group.

In a retrospective study, Alkayed et al. (26) evaluated the relationship of blood products transfusion with EFS and OS. Analyses were performed on the transfusion of PRBC and single donor platelets (SDPs) during the induction phase of chemotherapy. The participants were 136 ALL patients under 19 years of age. The HR values of PRBC for OS and EFS were 1.03 and 1.02, respectively (95% CI: 0.83-1.27, P = 0.76 and 95% CI: 0.85-1.24, P = 0.76, respectively). Also, the HR values of SDP for OS and EFS were 0.98 and 1.03, respectively (95% CI: 0.80-1.20, P = 0.87 and 95% CI: 0.90-1.18, P = 0.64, respectively). The analysis of the frequency of blood products transfusion with OS and EFS showed that the patients who received blood more than three times had a 4-year OS and a 4-year EFS of 85% and 50%, respectively (p-values = 0.19 and 0.12).

In a retrospective observational study, Jaime-Pe´rez et al. (28) assessed the relationship of the number and type of blood transfusions with OS and event-free survival EFS in 108 ALL patients aged 0 to 15 years. They divided the patients into the three groups of without transfusion, 1-5 PRBC transfusions, and more than five PRBC transfusions. The most significant association was observed between survival reduction and PRBC transfusion of more than five times. The HR of PRBC transfusion more than five times for relapse and death were 3.13 and 4.45, respectively (95% CI: 1.309-7.503, P = 0.010 and 95% CI, 1.64-12.09, P = 0.003, respectively). The HR of platelet transfusion for relapse and death were 2.40 and 5.22, respectively (95% CI: 0.983-5.899, P = 0.055 and 95% CI: 2.12-14.26, P <0.001, respectively).

In fact, transfusion of blood products is like transplantation of allogeneic liquids, which is associated with immunological alterations in patients. As reported, blood products transfusion is accompanied with increased risks such as bacterial infections, recurrence of disease, and mortality (29). Importantly, the role of blood transfusion in the prognosis of ALL children is not fully elucidated (28).

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In this research, CD34-negative patients had higher platelets counts at admission and received a less quantity of platelets during chemotherapy. In fact, the need for more platelets was a good prognostic factor for those patients. This result is inconsistent with the study by Almasi-Hashiani et al. (30), but it is justifiable to the relatively small population of in the present study and the little variation of the patients. Although CD34-positive patients had a lower Hb level at diagnosis, they had fewer PRBC transfusions during chemotherapy. Therefore, CD34 positivity was a good prognostic factor for these patients. The CD34-positive patients had a relatively higher level of ANC at admission, were hospitalized less frequently due to febrile infection, and experienced shorter hospital stay. Therefore, CD34 positivity was a good prognostic factor for this group.

Conclusion

This study focused on the role of the CD34 marker in children with B-ALL as well as its relationship to the prognosis of those patients during and after chemotherapy. Among the affected children, the CD34-positive cases had better prognosis than the CD34-negative ones in terms of both blood products transfusion (except for platelets) and the frequency and duration of hospitalization due to febrile infection. One of the limitations of this study was its retrospective design. So, the cause and effect relationship is not provable, and prospective studies are needed. Also, the relatively small sample size and the research in a single center make it somehow difficult to generalize the findings on the patients.

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Conflict of interest

The authors declare no conflict of interest.

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