Is Cd11c and Fmc7 Negativity in Chronic Lymphocytic Leukemia Poor Prognostic?

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Abstract Chronic lymphocytic leukemia (CLL) is a common hematological malignancy. This study is aimed to investigate the prognostic effect of clinic, laboratory and flow cytometric analysis in CLL patients. Newly diagnosed 55 CLL cases were divided into two groups, as stable disease (Group 1) and progressive disease (Group 2). Group 1 included those who did not require any treatment since diagnosis and those who did not progress after receiving the first step anti CLL treatment. Group 2 included the patients who received ≥ 2 steps treatment. The relation between the two groups was analyzed statistically in terms of clinical, laboratory and flow cytometric findings. Twenty patients (36.3%) required treatment at the time of diagnosis, four patients (3.8%) received first-line treatment during follow-up and 31 (56.3%) patients were followed without any treatment. Thirteen patients required second step treatment after a median of 26.3 months. The risk of progression was found to be increased 5-fold ($p = 0.015$) in the CD38 positive patient group, 4.2-fold ($p = 0.0147$) in the FMC7 negative patient group and 2.8-fold in the CD11c negative patient group. FMC 7 negativity decreased total survival 5.9-fold ($p = 0.051$). Unlike similar publications, we found that patients with CD11c or FMC7 negativity were in a higher need for ≥ 2 step treatment. This suggests that CD11c or FMC7 negativity may be used as a poor prognostic marker in CLL.

Keywords CLL · Flowcytometry · FMC7 · CD11c

Introduction

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative hematological malignancy characterized by a progressive increase in monoclonal B lymphocytes. CLL is more common in elderly population, median age is 70 years at diagnosis [1]. Clinical and laboratory findings of CLL patients are highly variable during diagnosis. Most of the cases with CLL are referred to the clinics with incidentally detected absolute lymphocytosis on routine health check up whereas a few are referred with B symptoms, lymphadenopathy or organomegaly [2, 3]. CLL diagnosis is based on the demonstration of B lymphocyte monoclonality in flow cytometric analysis of peripheral blood mononuclear cells in patients with absolute lymphocyte counts $\geq 5000/\mu\text{L}$ [4]. In CLL patients, there can be increased frequency of infections due to acquired immunodeficiency. Besides, autoimmune complications like hemolytic anemia, immune thrombocytopenia and pure red cell aplasia can be seen [5].

In CLL, lymphocytes have more than one B cell surface antigen (CD19, CD20, CD21, CD23, and/or CD24) and one type of surface immunoglobulin light chain expression with T cell CD5 surface antigen expression [6]. FMC7, CD22 and CD79b are also frequently negative or weakly expressed [7]. In typical CLL, there is CD5 and CD19 coexpression. Clinical course can be quite variable in CLL patients. Most cases are followed up without treatment, while in others, requirement for treatment emerge more rapidly. Therefore, it is important to determine prognostic parameters affecting the disease course at the onset. CLL prognosis is known to be worsely affected by the advanced

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stage (III and IV) of the disease, lymphocyte doubling time (less than 6 months), genetic abnormalities such as 17p deletion, presence of unmutated immunoglobulin heavy chain variable regions and high beta 2 microglobulin level [8–13]. The recently developed CLL-IPI prognostic scoring system which includes age, clinical stage, del 17p status, β 2 microglobulin level and IGVH mutation is used for this purpose [14]. There are multiple studies examining the prognostic effect of various cell surface markers. Flow cytometric analysis of CLL lymphocytes such as CD38 and ZAP70 positivity have been shown to be associated with poor outcome [15–17]. FMC7 is a monoclonal antibody in glycoprotein structure that is frequently expressed on normal mature B lymphocytes. There are studies associating FMC7 expression with atypical CLL [18]. CD11c positivity is defined as aberrant expression in CLL [19]. In this study, we aimed to determine the association of immunophenotypical characteristics found on flowcytometry and the disease course in CLL.

Materials and Methods

Patients

The data of 55 patients diagnosed with CLL between 2009 and 2015 were retrospectively reviewed. The time from diagnosis to disease progression or death, whichever happened first, was considered as progression-free survival. The patients were divided into two groups, as stable disease (Group 1) and progressive disease (Group 2). Group 1 included those who did not require any treatment since diagnosis and those who did not progress after receiving the first step CLL treatment. Group 2 included the patients who required ≥ 2 steps treatment.

Flow Cytometry

Blood/bone marrow samples in 4 mL K3 EDTA tubes (BD Vacutainer®, CA) were used as flow cytometry samples and studied rapidly. The cell surface markers of the samples were labeled with monoclonal antibodies using a stain-lyse-and-then-wash direct immunofluorescence method. Beckman Coulter (BC, USA) was supplied for the monoclonal antibodies used in labeling in flow cytometry. Monoclonal antibodies containing fluorescein isothiocyanate (FITC), phycoerythrin (PE), phycoerythrin-t xas-red (ECD), phycoerythrin cyanin5 (PC5), allophycocyanin (APC) were used in all patients: CD45/CD5/CD10/CD19/CD23, CD19/CD103/CD22/CD11c/CD25/CD5/CD20/sIg κ /sIg λ /CD45, CD19/CD3/CD79b/CD22 and CD19/CD43/CD200/CD38, ZAP-70 expression. Instrument alignment was confirmed daily using an alignment control bead

(Flow-Check, BC, USA). The accuracy and precision of cell count were tested using international quality controls purchased from the United Kingdom National External Quality Assessment Scheme (UK NEQASLI, Sheffield, UK) (z score range – 2.0 to 2.0). Briefly, CD19+ B cells were selected (at least 2000 events according to the threshold of the isotype control) from the data file using conventional gating strategies (forward and side scatter and the pattern of CD19 expression). The cut-off value for surface markers (excluding CD11c) was taken as 30% and surface marker expression $\geq 30\%$ was considered positive and $< 30\%$ was considered negative. Due to the aberrant expression of CD11c on CLL lymphocytes, 20% was considered as the cut-off value for CD11c expression. The relationship of the clinical and flow cytometric findings between the two groups was analyzed statistically.

Statistics

SPSS (Statistical Package for Social Sciences) version 17.0 for windows was used. Chi-squared test or Mann–Whitney U test were used to compare the differences between demographic, clinical and laboratory variables. Log-rank test was used for statistical comparisons. Receiver operating characteristic (ROC) curves were formulated to estimate a cut-off of CD38, CD11c and FMC7 for progression free survival. Cox Proportional Hazards Model was used for multivariate analysis. Kaplan–Meier's curves were used for survival analysis. A two-sided *p* value < 0.05 was considered statistically significant.

Results

The mean age was 66.5 ± 11.3 and 30 (54%) patients were over 65 years old. The number of male and female patients were 41 (74.5%) and 14 (25.5%), respectively. At diagnosis, 42 patients had early stage (RAI 0/I/II) disease while 13 patients had advanced stage (RAI III/IV) disease. Twenty patients (36.3%) required treatment at the time of diagnosis, four patients (7.2%) received first-line treatment during follow-up and 31 (56.3%) patients were followed without any treatment. Median follow up time was median 57 (28.8–85.1) months. Thirteen patients (23.6%) required second step treatment after a median of 26.3 months. At the time of diagnosis, 16 (29.1%) patients had anemia, 10 (18.2%) patients had thrombocytopenia, 17 (30.9%) patients had B symptoms, 10 (18.2%) patients had direct coombs positivity. Two patients (3.6%) developed autoimmune thrombocytopenia and three (5.5%) patients developed autoimmune hemolytic anemia. Two (3.6%) patients developed Richter's transformation. Five patients (9.1%) died during the follow-up. There were 24 patients

who were treated with 1st step. The total number of first step treated patients were included the cases who received first treatment either at diagnosis ($n = 20$) or during follow up ($n = 4$). There were 21 (38.2%) cases with CD38 positive and 10 (47.6%) of them received first-line treatment. There were 12 (21.8%) patients with FMC7 negative and 6 (50%) of them received first-line treatment. There were CD11c negative 32 (58.2%) cases and 8 (25%) of them received first-line treatment either at diagnosis or during follow-up.

The data of 42 patients in Group 1 and 13 patients in Group 2 were compared. The clinical and laboratory findings of the patients in group 1 and group 2 at the time of initial diagnosis is given in Table 1. Advanced age (> 65 years) 10.5 fold ($p = 0.024$), anemia 5.7 fold ($p = 0.002$), thrombocytopenia 3 fold ($p = 0.056$), advanced stage disease 4.4 fold ($p = 0.008$), splenomegaly 6.6 fold ($p = 0.004$) times increased the requirement of ≥ 2 steps treatment. Tables 2 and 3 summarize the factors affecting progression-free survival. The risk of progression was found to be 5.1-fold ($p = 0.015$) in the CD38 positive patient group. If 34% cut-off was accepted for CD38, the requirement for treatment increased 6.6-fold ($p = 0.004$) with 95% CI (1.8–24.36). In CD11c negative group when

20% cut-off was accepted, disease progression increased 2.8-fold ($p = 0.009$ and 95% CI (0.85–9.1). In the FMC7 negative group, the requirement for treatment was increased by 4.2 ($p = 0.017$) fold and total survival decreased by 5.9-fold ($p = 0.051$) in this group. When 43.5% cut-off was accepted for FMC7 negativity, total survival was reduced by 12.8-fold [$p = 0.022$ and 95% CI (1.4–115)]. There was no statistically significant correlation between CD5, CD19, CD23, CD20, CD22, CD43, CD79b expression and progression. There were 5 patients with CD38 + CD11c-FMC. All of these cases had first-step treatment in the diagnosis. In the follow-up, ≥ 2 steps treatment was applied in 4 (80%) of these cases. The characteristics of patients who required ≥ 2 step treatment (Group 2) is given in Table 4. Progression-free survival in this patient group was median 37 (11.2–62.7) months ($p = 0.012$). Progression-free survival of 50 patients without this group was median 57 (24.2–89.7) months ($p = 0.012$).

Table 1 Demographic features of patients (Group 1, Group 2) at the initial diagnosis time

Clinical findings of patients	Group 1 (n: 42, %/n)	Group 2 (n:13, %/n)
≤ 65 years old	25 (59.5%)	5 (38.4%)
> 65 years old	17 (40.4%)	8 (61.5%)
Gender		
Male	30 (71.4%)	11 (84.6%)
Female	12 (28.5%)	2 (15.3%)
RAI stage		
RAI stage 0/I	37 (88%)	5 (38.4%)
RAI stage 2/3/4	5 (12%)	8 (61.5%)
Presence of B symptom	11 (26.1%)	6 (46.1%)
Presence of anemia	6 (14.2%)	10 (76.9%)
Presence of thrombocytopenia	2 (4.7%)	8 (61.5%)
Splenomegaly	11 (26.1%)	9 (69.2%)
Hepatomegaly	8 (19%)	3 (23%)
Immune hemolytic anemia	1 (0.02%)	0 (0%)
First line therapy in initial diagnosis time	20 (47.6%)	7 (53.8%)
CD38 positive patients	11 (26.1%)	10 (76.9%)
FMC7 negative patients	6 (14.2%)	6 (46.1%)
CD11c negative patients	21 (50%)	9 (69.3%)
Hemoglobine (g/L) (min–max)	13.3 g/L (7.80–17.50 g/L)	10.6 g/L (8.2–14.8 g/L)
White blood cell ($\times 10^6$ cells/L) (st.s)	14,900 (1700–13,400)	25,000 (15,600–106,000)
Platelets ($\times 10^6$ cells/L) (min–max)	191,000 (10,000–335,000)	128,000 (10,000–250,000)
LDH (g/L) (st.s)	229 (± 29)	268 (± 19)
Beta 2 microglobulin (mg/dL) (min–max)	2.47 (2.1–7.3)	2.68 (1.9–8.5)

The p values of the parameters written in bold color < 0.005

Table 2 Descriptive values and comparison results for progression free survival

	PFS (Months) Mean $\pm$ SE*	<i>P</i> **
Age		
< 65	53.00 $\pm$ 8.48	
> 65	46.54 $\pm$ 9.12	0.002
Hemoglobin level (g/dL)		
> 11	70.82 $\pm$ 9.42	
< 11	25.36 $\pm$ 5.49	0.001
Thrombocytopenia		
No	66.18 $\pm$ 9.09	
Yes	28.06 $\pm$ 6.04	0.044
LDH (μ L)		
> 200	55.20 $\pm$ 6.08	
< 200	54.75 $\pm$ 9.34	0.193
RAI stage		
0, I, II (early)	68.82 $\pm$ 9.32	
III, IV (late)	27.16 $\pm$ 5.73	0.004
Splenomegaly		
No	88.23 $\pm$ 5.32	
Yes	31.24 $\pm$ 3.87	0.005
Treatment at diagnosis		
No	88.13 $\pm$ 7.37	
Yes	33.27 $\pm$ 5.47	0.001
CD38		
Positive	29.89 $\pm$ 4.02	
Negative	56.67 $\pm$ 4.53	0.007
FMC7		
Positive	52.17 $\pm$ 4.71	
Negative	25.67 $\pm$ 8.05	0.009
CD11c		
Positive	50.1 $\pm$ 3.8	
Negative	20.4 $\pm$ 6.8	0.009
Zap70		
Negative	49.06 $\pm$ 5.60	
Positive	9.33 $\pm$ 0.72	0.034

The *p* values of the parameters written in bold color < 0.005 and it's statistically significant

*Kaplan–Meier survival analysis

**Log-Rank test

Discussion

Clinical course can be quite variable in CLL patients. Most cases are followed without treatment, while in others, requirement for treatment emerge more rapidly. Therefore, prognostic parameters affecting the disease course might be important to determine initially. CLL prognosis is known to be worsely affected by the advanced stage (III and IV) of the disease, lymphocyte doubling time (less than

Table 3 Hazard ratio of the factors affecting the PFS

	RR	95% CI	<i>P</i> *
Age			
< 65 (R)			
> 65	10.502	1.354–81.453	0.024
Hemoglobin (g/dL)			
> 11 (R)			
< 11	5.78	1.861–17.952	0.002
Thrombocytopenia			
Yes			
No (R)	3.008	0.973–9.299	0.056
LDH (μ L)			
> 200 (R)			
< 200	2.645	0.578–12.101	0.210
RAI stage			
0, I, II (early) (R)			
III, IV (late)	4.402	1.464–13.234	0.008
Splenomegaly			
No (R)			
Yes	6.629	1.459–30.110	0.014
Treatment at diagnosis			
Not started (R)			
Started	3.268	1.001–10.665	0.050
CD38			
Negative (R)			
Positive	5.117	1.378–19.011	0.015
FMC7			
Positive (R)			
Negative	4.265	1.295–14.042	0.017
CD11c			
Positive (R)			
Negative	2.79	0.85–9.1	0.009
Zap70			
Negative (R)			
Positive	5.515	0.918–33.143	0.062

The *p* values of the parameters written in bold color < 0.005 and it's statistically significant

*Cox's proportional hazard regression

6 months), genetic abnormalities such a 17p deletion, presence of unmutated immunoglobulin heavy chain variable regions.

The clinical parameters shown to be prognostic in this study were age and presence of anemia and thrombocytopenia. In our study, we found that PFS of older patients (> 65 years) was significantly shorter than younger patients. There are many reports showing that advanced age reduces the survival and is a poor prognostic factor in CLL. Fragility and poor treatment tolerance in advanced age also contributes to worsening prognosis [20–22]. Presence of anemia or thrombocytopenia which is

Table 4 Characteristics of patients who required ≥ 2 step treatment (Group 2)

Cases	Age/sex	Stage (RAI)	Treatment indication	CD38, CD11c, FMC7, ZAP70
Case 1	64/M	0	B symptoms/short lymphocyte doubling time	Negative, negative, positive, negative
Case 2	70/M	3	B symptoms/short lymphocyte doubling time	Positive, negative, negative, negative
Case 3	59/M	1	B symptoms	Positive, negative, negative, negative
Case 4	75/M	2	Stage progression	Positive, negative, negative, negative
Case 5	65/M	1	Stage progression	Positive, negative, positive, negative
Case 6	89/M	2	B symptoms, Compression symptoms	Positive, positive, negative, positive
Case 7	51/M	3	Stage progression	Positive, negative, negative, negative
Case 8	60/M	2	Short lymphocyte doubling time/organomegaly	Positive, positive, positive, negative
Case 9	86/M	2	Compression symptoms	Positive, positive, positive, positive
Case 10	59/M	1	Compression symptoms	Negative, negative, positive, negative
Case 11	82/F	3	Stage progression	Positive, negative, negative, negative
Case 12	77/M	2	B symptoms	Positive, positive, positive, positive
Case 13	56/F	1	Stage progression/B symptoms	Negative, negative, positive, negative

associated with advanced stage are known poor prognostic factors in CLL [23].

Unlike similar studies, in our study progression-free survival was reduced in cases with FMC7 negativity and/or CD11c negativity. Similar to the literature, CD38 positivity, advanced age, advanced stage, anemia and thrombocytopenia increased the frequency of disease progression.

CD11c is an adhesion molecule that is a member of the integrin family. CD11c plays a role in cellular activation steps in cells [24]. CD11c is mainly expressed in higher levels in dendritic cells, but also expressed in lower levels in granulocytes, monocytes, NK cells and activated T and B cells [25]. The presence of CD11c is known as aberrant expression in CLL cases because CD11c is normally expressed in hairy cell leukemia [19]. CD11c expression is found in 49% of CLL and 57% of B cell Non-Hodgkin's lymphoma. Clinical findings and prognostic relevance of CD11c in CLL is limited. In a recently published study involving 151 cases, there was a significant relationship between CD11c positivity ($\geq 20\%$) and time till treatment [26]. In our study, we found that CD11c negativity (cut off 20% below) reduced progression-free survival.

FMC7 is considered to be a potent surface antigen that can be used to differentiate CLL from other B cell lymphomas. In particular, it is a surface antigen that is used to distinguish the mantle cell lymphoma from CLL [18]. In some atypical CLL cases FMC7 expression can be positive [27]. In literature FMC7 negativity is a typical finding in CLL patients during diagnosis [28]. Even though FMC7 negativity is a common finding in CLL, we found that if the cut-off value is set to 30% and the negative expression is considered below 30%, these patients required treatment

more often. We also found that when we accept cut off of 43.5% for FMC7 negativity, total survival is reduced by 12.8 times. The literature on this subject is limited. In a study with a cut-off value of 10% in FMC7 positivity, there was a positive correlation between FMC 7 positivity and complex karyotype status [29].

CD38 is a transmembrane glycoprotein expressed on the surface of leukemic cells. In CLL, CD38 positivity is known to be a poor prognostic marker associated with treatment resistance, shorter time to first treatment, and short surveillance [30, 31]. In one study, it is suggested that CD38 expression greater than 20% is associated with lymph node involvement, low hemoglobin level, hepatomegaly and high beta 2 microglobulin levels and also associated with an aggressive clinical course [32]. In another study, CD38 positivity was associated with event free survival and total survival in advanced stage cases, whereas CD38 positivity in early stage cases was found to be a poor prognostic factor associated with short survival. In previous studies, there are publications that accept cut-off values of 30% and 20% for CD38 [33, 34]. Similar to the previous studies in the literature CD38 positivity was associated with progression in our study.

According to our study, in CD11c and/or FMC7 negative patients an increase in the need for treatment suggests that negative markers may be used as a poor prognostic factor. Planning large number case studies on this subject will be appropriate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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