Role of CD200 and CD43 in Diagnosis and Prognosis of CLL and NHL Patients

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Abstract— **Background: Chronic lymphoproliferative disorder (LPD), is a malignant disease of lymphocytes in the blood and lymphatic tissue. Chronic lymphocytic leukaemia, it is the commonest type of chronic lymphoproliferative disorder.**

Scoring by immunophenotyping is used to differentiate B-cell chronic lymphocytic leukemia from other B-Non-Hodgkin lymphomas. CD200 (OX2) is a glycoprotein of membrane, it is related to type I superfamily of immunoglobulin .

CD43 (Sialophorin) is a sialoglycoprotein that is present on the surface of T lymphocytes, some B lymphocytes, granulocytes and monocytes, that play important role for immune function and also play a role as physiologic ligand-receptor complex involved in T-cell activation.

Aim of study-Evaluate the role of CD200 and CD43 positive expression and co-expression in diagnosis and prognosis of CLL and NHL.

Subjects and Methods: This cross sectional study on one hundred forty five patients with chronic lymphoprliferative disorders who were attending Baghdad teaching hospital at medical city from beginning of January 2020 to end of December 2020, patients divided in to two groups; chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) patients At diagnosis, there was assessment of CD200 and CD43. Clinical and laboratory data were done including staging by modified Rai, and Ann arbor staging system (for CLL and NHL respectively), then follow up for about 6-12.

Results: There is significant statistical correlation between CD 200 and CD 43 and often co-expression of both in differentiation between CLL and NHL (p value < 0.001).

Almost all patients of CD 200 positive expression show moderate to bright pattern of expression in CLL in apposite to NHL patients, who showed dim to moderate pattern of expression, while the great majority of CD43 expression was dim to moderate pattern in both CLL and NHL patients.In CLL patients there was no significant correlation between prognostic markers (age, Hb, platelets count, lymphocytes count and CD 38 expression) and CD200, CD 43.

For NHL patients, all markers show no significant correlation except that CD 43 show significant correlation with expression of CD 38.

Conclusion: CD200, CD43 and often co-expression of both have a significant value in diagnosis and differentiation of CLL from B-NHLs.

I. Introduction

This chronic lymphoproliferative disorder (LPD), is a malignant disorder of lymphocytes in blood and lymphatic tissue. Chronic lymphcytic leukaemia is the commonest chronic lymphoproliferative disorder (LPD) (1). It is frequently diagnosed by combination of clinical, cytogenetic and immunophenotyping (2). Meanwhile, some of CLL cases still unclear because the cytological and flowcytomertic markers can overlay with other lymphoproliferative diseases that present with leukemic phase (3). Many efforts have been made to use immunophenotypic markers by flowcytometry or called scoring system that greatly help to differentiate between CLL and NHL, till now, there is no single test that can clearly differentiate between them (4).

Scoring system by flowcytometry is used to differentiate B-cell chronic lymphocytic leukemia (B-CLL) from B-NHLs. expression of CD23, CD5 and absent or weak expression of CD79b , FMC7, also weak expression of surface IgM make the score is five. However, cases diagnosed as B-NHL had intermediate score of (2–3 points) (3). So scoring by flowcytometry is an important tool in the diagnostics of B-cell non-Hodgkin lymphomas (B-NHLs). The European Research Initiative on CLL implication for flow cytometry, they add another important markers like CD43, CD81, CD200, CD10 and ROR1 for differential diagnosis of CLL and low grade B cell lymphoma (5).

CD200 (OX2) it is a glycoprotein of cell membrane and belongs to the type I superfamily of immunoglobulin. It is usually found or expressed on many of human cells including T and B lymphocytes (6).

CD43 (Sialophorin) it is a sialoglycoprotein on the top of human T lymphocytes, B lymphocytes, granulocytes and monocytes, that play an important for immunity and act as physiologic ligand-receptor complex involved in T-cell activation (7).

The aims of study:

Evaluate the role of CD200 and CD43 positive expression and co expression in diagnosis and prognosis of CLL and NHL patients

II. Patient , Materials And Method

A. Patients

1. Study subject

This study including 145 patients diagnosed CLL and leukaemic phase of NHL through January to December 2020. Those patients were collected from hematology department in Baghdad teaching hospital, the immunophenoptyping done by 8 colour flowcytometery. The diagnosis depend on clinical data, blood film and bone marrow examination which showed absolute lymphocytosis of mature morphology, then immunophenotypic analysis by flowcytometry with MS scoring

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was done for diagnosis of chronic lymphocytic leukaemia and non-Hodgkin lymphoma, CD38 expression was also measured in addition to CD200 and CD43 which are the main markers on the study. At diagnosis, clinical information including age, gender, clinical examination such as organomegaly, generalize or localize lymphadenopathy were obtained from patient laboratory case sheet. According to hematological parameters, physical and clinical findings we made staging for each patient in order to make good categorization for patient stage and the future response to treatment. So for CLL patients we use modified Rai staging system to differentiate low, intermediate and high risk group. For NHL patients we depend on ann arbor staging system, also to make categorization of patient in to four staging group in which there are four groups (I,II,III,IV). All patient were evaluated there after either by face to face collection of data on their attendance to hospital or by phoning, follow up program including all patients (on treatment or those whose physician prefer to not use treatment) for six to twelve months, evaluation of their hematological, clinical and physical response and assessment of their remission state depending on blood film, bone marrow finding and some patient with detection of minimal residual disease by flowcytometry was done.

2. Inclusion criteria

1-Newly diagnosed mature B- cells neoplasm.
2-The patient are randomly collected in relation to gender.
3-Adult group patients.
4-All patient were not receive any treatment before sample collection.

3. Data Analysis

Statistical analysis was carried out using SPSS version 25. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Student t-test was used to compare means between two groups. Mann-Whitney Test was used to compare means between two groups when variable was not normally distributed. Pearson chi-square and Fisher's exact test were used to find the association between categorical variables. A *p*-value of ≤ 0.05 was considered as significant.

III. The Results

A. The study groups

This is across sectional study including 145 LPD patients diagnosed by flowcytometry in to two main subtypes, 98 patients with CLL and 47 patients with NHL have mean age of 62.73 and 62.1 years respectively. Male is more than female percentage as in table (1).

B. Age and sex distribution

Table 4.1: The association between socio-demographic characteristics and diagnosis (N=145)

Study variables	CLL (N=98)	NHL (N=47)	P-value
Age (years)	(62.73 ± 9.20)	(62.10 ± 10.25)	0.711
Gender			
Male	61 (62.2)	32 (68.1)	0.493
Female	37 (37.8)	15 (31.9)	
Total	98 (100.0)	47 (100.0)	

IV. Role of CD200 and CD43 in differentiation between CLL and NHL.

A. The relevance of each CD marker in diagnosis of CLL and NHL

There was significant association between study variables including (CD200 and CD43) and diagnosis, CD200 and CD43 are positive in high percentage of CLL patients, p value below 0.001, as shown in table (2)

Table 4.2 Association between study variables (CD200, CD43 and CD 305) and diagnosis (N=145)

Study variables	Diagnosis		Total	X^2	P-value
	CLL	Non Hodgkin Lymphoma			
CD 200					
Positive	98 (100.0)	29 (61.7)	127 (87.6)	**42.85**	**<0.001***
Negative	0 (0.0)	18 (38.3)	18 (12.4)		
Total	98 (100.0)	47 (100.0)	145 (100.0)		
CD 43					
Positive	82 (83.7)	15 (31.9)	97 (66.9)	**38.42**	**<0.001***
Negative	16 (16.3)	32 (68.1)	48 (33.1)		
Total	98 (100.0)	47 (100.0)	145 (100.0)		

B. The significance of co-expression CD 200 and CD 43 in CLL and NHL cases

There is significant positive co-expression of both CD200 and CD43 and diagnosis of CLL, p value below 0.001 as shown in table 3.

Table 4.3. Association between CD200 and CD43 co-expression and diagnosis (N=145)

Study variables	Diagnosis		Total	P-value
	CLL (98)	NHL (47)		
Positive CD 200 and CD 43 co-expression	82 (83.7)	9 (19.1)	91 (62.8)	**<0.001***

C. Association of pattern of expression and diagnosis

There is significant correlation between pattern (bright, moderate and dim) expression of CD200 and the provisional diagnosis with moderate to bright expression in CLL, p value below 0.001, as in figure 1

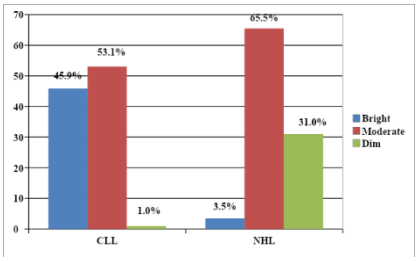

Figure 4.1: Distribution of patients with positive CD200 according to flow cytometry pattern of positive (N=127, P<0.001*)

There is no significant correlation between pattern (bright, moderate and dim) expression of CD43 and the provisional diagnosis, p value 1.000.as in figure 2.

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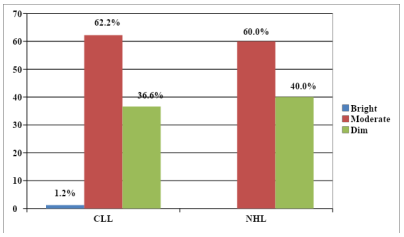

Figure 4.2: Distribution of patients with positive CD43 according to flow cytometry pattern of positive (N=97, P=1.000

D. Role of CD 200 and CD 43 in prognosis of CLL patients

There is no significant association between CD200 ,and CD43 with age, Hb. Level, platelets, lymphocytes count and CD38 in CLL patients as in table (4)

Table 4.4. Association between study variables (CD200, CD43) and laboratory prognostics factors in CLL patients (N=98)

Prognostic factors	CD 200			CD43		
	+ (98)	- (0)	P	+ (82)	- (16)	P
Age < 60 ≥ 60	36 (36.7) 62 (63.3)	0 (0.0) 0 (0.0)	-	30 (36.6) 52 (63.4)	6 (37.5) 10 (62.5)	0.945
Hb < 11 ≥ 11	46 (46.9) 52 (53.1)	0 (0.0) 0 (0.0)	-	40 (48.8) 42 (51.2)	6 (37.5) 10 (62.5)	0.408
Platelet count <100 ≥ 100	11 (11.2) 87 (88.8)	0 (0.0) 0 (0.0)	-	8 (9.8) 74 (90.2)	3 (18.8) 13 (81.2)	0.381
CD 38 Positive Negative	13 (13.3) 85 (86.7)	0 (0.0) 0 (0.0)	-	9 (11.0) 73 (89.0)	4 (25.0) 12 (75.0)	0.218
Lymphocyte < 30 ≥ 30	56 (57.1) 42 (42.9)	0 (0.0) 0 (0.0)	-	47 (57.3) 35 (42.7)	9 (56.2) 7 (43.8)	0.937

Relation to clinical stage of disease

. CD200 and CD43 has no significant relation to clinical stage as shown in table (5).

Table 4.5. Association between study variables (CD200, CD43) and clinical stage among CLL patients (N=98)

Study variables	Clinical Stage					Total	X^2	P-value
	Low risk (0) (8.2%)	Intermediate risk		High risk				
		I	II (56%)	III	IV (35.7%)			
CD 200 Positive Negative Total	8 (100.0) 0 (0.0) 8 (100.0)	31 (100.0) 0 (0.0) 31 (100.0)	24 (100.0) 0 (0.0) 24 (100.0)	23 (100.0) 0 (0.0) 23 (100.0)	12 (100.0) 0 (0.0) 12 (100.0)	98 (100.0) 0 (0.0) 98 (100.0)	-	-
CD 43 Positive Negative Total	8 (100.0) 0 (0.0) 8 (100.0)	26 (83.9) 5 (16.1) 31 (100.0)	19 (79.2) 5 (20.8) 24 (100.0)	20 (87.0) 3 (13.0) 23 (100.0)	9 (75.0) 3 (25.0) 12 (100.0)	82 (83.7) 16 (16.3) 98 (100.0)		0.652 f

Relation to state of remission

35% of CLL patients not need treatment, as shown in figure (4) CD200 and CD43 had neither association to clinical stage of disease nor to remission state after treatment.

Table 4.6. Association between study variables (CD200, CD43) and state of remission in CLL patients (N=98)

Study variables	State of remission				Total	P-value
	Patients die while on treatment	Patients have treatment without remission	Patients have treatment with remission	Patients not need treatment		
CD 200 Positive Negative Total	9 (100.0) 0 (0.0) 9 (100.0)	14 (100.0) 0 (0.0) 14 (100.0)	41 (100.0) 0 (0.0) 41 (100.0)	34 (100.0) 0 (0.0) 34 (100.0)	98 (100.0) 0 (0.0) 98 (100.0)	-
CD 43 Positive Negative Total	7 (77.8) 2 (22.2) 9 (100.0)	11 (78.6) 3 (21.4) 14 (100.0)	33 (80.5) 8 (19.5) 41 (100.0)	31 (91.2) 3 (8.8) 34 (100.0)	82 (83.7) 16 (16.3) 98 (100.0)	0.468

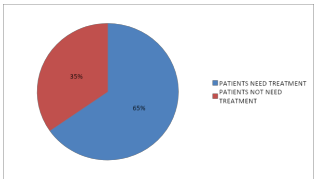

Figure 4.4. Show number of CLL patients who need treatment 64 (65%), and those who not need 34 (35%) total number 98 patients.

E. Role of CD 200, CD43 in prognosis of NHL patients

Association with laboratory factors

There is no significant association between CD200 , CD43 with age, platelets, lymphocytes count in NHL patients , p value 0.03 as in table (7).

Table 4.7. Association between study variables (CD200, CD43) and laboratory prognostics factors in NHL patients (N=47)

Prognostic factors	CD 200			CD43		
	+ (29)	- (18)	P	+ (15)	- (32)	P
Age < 60 ≥ 60	12 (41.4) 17 (58.6)	4 (22.2) 14 (77.8)	0.178	6 (40.0) 9 (60.0)	10 (31.3) 22 (68.7)	0.555
Hb < 11 ≥ 11	14 (48.3) 15 (51.7)	11 (61.1) 7 (38.9)	0.391	9 (60.0) 6 (40.0)	16(50.0) 16 (50.0)	0.522
Platelet count <100 ≥ 100	8 (27.6) 21 (72.4)	3 (16.7) 15 (83.3)	0.492	5 (33.3) 10 (66.7)	6(18.8) 26 (81.2)	0.292
CD 38 Positive Negative	6 (20.7) 23 (79.3)	2 (11.1) 16 (88.9)	0.692	6 (40.0) 9 (60.0)	2 (6.3) 30 (93.7)	**0.009***
Lymphocyte count	17.18	30.11	0.347	12.58	26.61	0.268

Relation to clinical stage of disease

CD200 and CD43 has no significant role as shown in table (8).

Table 4.8. Association between study variables (CD200, CD43 and CD305) and clinical stage among non-Hodgkin lymphoma patients (N=47)

Study variables	Clinical Stage				Total	P-value
	Low risk		High risk			
	I	II (27.7%)	III	IV (72.3%)		
CD 200 Positive Negative Total	1 (100.0) 0 (0.0) 1 (100.0)	10 (83.3) 2 (16.7) 12 (100.0)	12 (50.0) 12 (50.0) 24 (100.0)	6 (60.0) 4 (40.0) 10 (100.0)	29 (61.7) 18 (38.3) 47 (100.0)	0.215
CD 43 Positive Negative Total	0 (0.0) 1 (100.0) 1 (100.0)	3 (25.0) 9 (75.0) 12 (100.0)	7 (29.2) 17 (70.8) 24 (100.0)	5 (50.0) 5 (50.0) 10 (100.0)	15 (31.9) 32 (68.1) 47 (100.0)	0.577

Relation to state of remission

CD43 negative expression correlated with achievement of remission state and with patients on no treatments, as shown in table (9) keeping in mind that 89% of NHL patients in this study were on treatment as in figure (5).

Table 4.9. Association between study variables (CD200, CD43) and state of remission in NHL (N=47)

Study variables	State of remission				Total	P-value
	Patients die while on treatment	Patients have treatment without remission	Patients have treatment with remission	Patients not need treatment		
CD 200 Positive Negative Total	5 (55.6) 4 (44.4) 9 (100.0)	12 (54.5) 10 (45.5) 22 (100.0)	7 (63.6) 4 (36.4) 11 (100.0)	5 (100.0) 0 (0.0) 5 (100.0)	29 (61.7) 18 (38.3) 47 (100.0)	0.336
CD 43 Positive Negative Total	3 (33.3) 6 (66.7) 9 (100.0)	11 (50.0) 11 (50.0) 22 (100.0)	0 (0.0) 11 (100.0) 11 (100.0)	1 (20.0) 4 (80.0) 5 (100.0)	15 (31.9) 32 (68.1) 47 (100.0)	**0.019***

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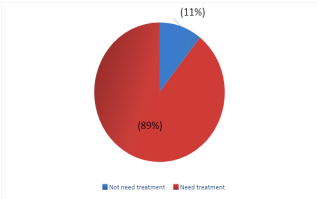

Figure 4.5. Show number of NHL patients who need treatment 42 (89%), and those who not need 5 (11%) total number 47 patients

DISCUSSION

A. Age and sex distribution in patients with CLL and NHL

In this study, mean age of CLL patients is 62.73 and NHL is 62.1, this goes with the fact that LPDs can affect elderly age group and has clear age preference (3). LPD has no sex predilection, and in this study, no significant sex difference between CLL and NHL patients, although most were male that account for (62%) in CLL, (68%) for NHL patients. This may be attributed to the sample size and random chance.

B. Expression of CD200, CD43 in diagnosis of CLL and NHL

We investigate the value of expression of CD200, CD 43 in diagnosis of LPDs

- CD200 was significantly positive in almost all patients in this study, with moderate to bright expression in all CLL (98/98) (100%), while in (NHL) patients CD 200 was mostly dim to moderate expression in 29 out of 47 patients (61.7%) (p value < 0.001) as in table 2, figure 1.

The explanation of the difference in expression patterns of CD200 in BCLPDs, literature partially mentioned this to the different activation of the AKT and MEK/ERK pathways in these different disorders (4).

- CD43 was expressed in (82/98) (83.7%) in CLL patients with dim to moderate expression while it was almost always dim - moderate expression in 15 out of 47 NHL patients (31.9%) (p value < 0.001) as show in table 2, figure 2, these findings are consistent with El Desoukey NA et al, Sandes AF et al, Alapat D et al, Brunetti L et al, Pillai V et al, McWhirter JR et al and Kohnke T et al; all those series show that almost all CLL cases show moderate to bright expression of CD200 and CD 43 with lower expression in those with NHL patients.(4, 5,40,48, 49, 50,51).

In this series of chronic lymphoproliferative disorders with exclusive PB and/or BM affection, CD43-positivity increased with increasing Matutes score of CLL, suggesting that this CD marker could be of help in the distinctive role in diagnosis of complex or borderline cases. The frequent CD43-positivity in CLL has been well recognized both by FC and our results agree with Sorigue M et al, Quijano S et al, Kostopoulos IV et al, Jung G et al. (7,52,53,58).

Other series show that CD43 improved the classification accuracy of the classical scoring system. However, the inclusion of CD43 offers a better performance that affect discriminant functions rather than the classical scoring system. So CD43, together with classical markers, is useful in differentiation between CLL and non-CLL, and should be systematically used in addition to well-known methods to improve the diagnosis and classification of the B-cell lymphoproliferative disorders (58).

-Co-expression of both 200 and 43 in differentiation between CLL and NHL; 82 with CLL out of 98(83.6%) of patients show co-expression of both CD200 and CD43 while 9 with NHL out of 47(19.1) of patients show both CD200 and CD43 markers expression, p value was significant (< 0.001) as show in table 3.

Some study state that the combination of CD200 and CD43 offers a highest accuracy to differentiate between CLL and non-CLL LPDs. However borderline LPDs, which constitute a small proportion of cases, remain a diagnostic challenge and cannot be dependably identified or readily diagnosed with our proposed combination of CD200 and CD43. but further studies will be necessary to determine a precise score (36).

We confirmed that the introduce CD200 and CD 43 to CLL matutes score system had a very high accuracy to distinguish between CLL and NHL patients(3).

C. Role of CD 200 and CD 43 as a prognostic parameter in CLL patients:

In this study, also we evaluate whether the use of CD200 and CD43 as an innovative routine marker could be helpful to improve the utility of flow cytometry in prognostic significance of CLL patients.

Prognostic factors can help us to sort CLL patients who need immediate therapy soon after diagnosis in which include certain clinical and laboratory features, cytogenetic, molecular, and biochemical characteristics of the neoplastic cell.

-CD 200 there is no significant statistical correlation between CD 200 expression and age, Hb, platelet count, lymphocytes count and CD38. Meanwhile about 86.7% of same group have negative expression of CD 38, which indicate good prognostic group (p value 0.037) as in table 4. the above parameters consider a prognostic laboratory features, these finding is consistent with El Desoukey NA et al and D'Arena G et al in whom state that CD200 expression in B-CLL was not correlated with these laboratory features (4,19); while in contrast to our results, Dorfman DM et al, El Din Fouad et al, Wang et al., Zahedi M et al and Wong KK conclude that positive CD200 expression was associated with these prognostic variable.(19,55,56,59,72) .

In present study we also notify that correlation of CD200 positive expression to the clinical stage of the disease that 35 out of 98 patients (35.7%) have high risk group (stage III-IV) while 63patients (64%) of them low and intermediate group (0-I-II) according to RIA staging system (there is no p value because all CLL patients was CD200 positive as in table 5, similarly El Desoukey NA et al and D'Arena G et al that consider the CD200 expression in B-CLL was not correlated with the clinical staging system (RAI staging) (4,34) while in contrast to our results, Dorfman DM et al, El Din Fouad et al, Wang et al., Zahedi M et al and Wong KK conclude that positive CD200 expression was associated with advanced stage and earlier time to progression .(19,55,56,59,72) .

There is no significant clinical association between CD200 expression and the state of remission as in table 6, this finding is consistent with El Din Fouad et al that conclude that there is

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no correlation with response to treatment and overall survival (55), as in table 6.

-CD 43 there is no significant statistical correlation between CD 43 expression and age, Hb, platelet count, lymphocytes count and CD 38, as in table 4.

also notify there is no significant correlation between CD43 expression and the clinical stage of the disease, as show in table 5.There are no significant clinical association between CD43 expression and the state of remission (p value 0.468) as show in 6.No other study correlate the expression of CD43 as a prognostic factor.

D. Role of CD200 and CD43 as a prognostic parameter in NHL patients

-CD200 there is no significant correlation between CD200 expression and the prognostic factors (age, Hb, platelet count, CD 38 expression and lymphocytes count) as in table 7, similarly El Desoukey NA et al, Sandes AF et al and Rodrigues et al (4, 5 and 68) .

Also there is no significant correlation between CD200 positive expression and clinical stage of the disease (p value 0.215) as in table 8.

Moreover There are no significant clinical association between CD200 expression and the state of remission (p value 0.336) as show in table 9, unfortunately there are no similar studies found to correlate these findings.

-CD43 there is no significant statistical correlation between CD43 expression and age, Hb, platelet count and lymphocytes count. While there is a significant correlation with presence of CD38 (which suggest poor prognostic value) (p value 0.009) as in table 7.

There is no significant association between CD43 and clinical stage of disease as in table 8, further studies are required to correlate CD43 with clinical stage.

There is significant correlation between CD 43 expression and state of remission, p value (0.019) so high percentage of patients 100%, 80% of patients achieved remission, not need treatment respectively show negative expression of CD43 as in table 9. so we conclude that CD 43 has negative expression in those with good prognostic history, this agreed with Ma XB et al that showed CD43 is an independent prognostic factor for DLBCL, NOS and other types of NHL that foresees poor prognosis, further studies are also recommended (26). further studies are required to verify our conclusions in other subtypes of NHL

CONCLUSION

From the present study, we may conclude the following:

1. CD 200 and CD43 expression and most commonly co-expression of both markers can significantly aid the diagnosis and discrimination of CLL from other B-LPDs.
2. CD200 has always moderate to bright expression in CLL while CD43 has dim to moderate expression.
3. CD200 and 43 expressions had no prognostic value for both CLL and NHL.
4. About 34.6% of CLL patients not need treatment.

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