Lymphoproliferative Disorders

research paper

haematologica 2002; 87:1021-1027
http://www.haematologica.org/2002_10/1021.htm

CD38 expression in B-cell chronic lymphocytic leukemia: association with clinical presentation and outcome in 155 patients

EVA DOMINGO-DOMÈNECH,* ALICIA DOMINGO-CLARÓS,° EVA GONZÁLEZ-BARCA,* DAVID BENEITEZ,* ESTER ALONSO,° VICENS ROMAGOSA,# SÍLVIA DE SANJOSÉ,@ JOSÉ PETIT,* ALBERT GRANENA,* ALBERTO FERNÁNDEZ DE SEVILLA*

*Department of Clinical Hematology; °Department of Cytology; #Department of Pathology; @Department of Epidemiology and Cancer Registry, Institut Català d'Oncologia and Hospital Princeps d'Espanya, Ciutat Sanitaria i Universitaria de Bellvitge, Barcelona, Spain

Correspondence: Eva Domingo Domènech, MD, Avda. Gran Via s/n, km 2.7. 08907 L'Hospitalet de Llobregat, Barcelona, Spain. Phone: international +34.9.32607812. Fax: international +34.9.34141630. E-mail: 31577edd@comb.es

Background and Objectives. To investigate whether CD38 expression at diagnosis is an independent predictor of survival and assess its associations with other clinical parameters used in the staging of B-cell chronic lymphocytic leukemia (B-CLL).

Design and Methods. CD38 expression was analyzed in 155 consecutive unselected patients newly diagnosed with B-CLL from January 1991 to July 1997. In all cases CD38 expression was evaluated at diagnosis and patients were classified into two groups: those with ≥ 30% were considered positive ($CD38^+$) and those with < 30% were considered negative ($CD38^-$). Statistical differences between each group were analyzed using χ^2 tests for categorical variables and Student's t-tests for continuous variables. Survival analysis was performed at the univariate level by the Kaplan Meier technique and at the multivariate level by Cox hazard models.

Results. Thirty (19%) patients were $CD38^+$. $CD38^+$ was associated with atypical morphology (p=0.004), a diffuse bone marrow pattern (p=0.016), Rai stage ≥2 (p=0.009), high lactate dehydrogenase (p=0.02), high β_2 microglobulin (p=0.004), and higher lymphocyte count (p=0.02). Furthermore, $CD38^+$ patients required treatment more frequently (p=0.006) and CLL-related mortality was significantly higher (p=0.012). When we divided the study group into patients with Rai 0-1 and Rai 2-4 stages, CD38 positivity was only significantly associated with mortality in the early stage patients (p= 0.012 vs p= 0.68). CD38 expression in the multivariate analysis lost its statistical significance. None of these results was modified when the CD38 cut-off was set at 20%.

Interpretation and Conclusions. CD38 expression identifies a subgroup of B-CLL patients with aggressive clinical presentation and worse outcome. Its expression is probably associated with other prognostic factors, but the feasibility of determining this parameter makes it easily reproducible and adds prognostic information at diagnosis to aid prediction of the clinical course and outcome of B-CLL.

Key words: B-CLL, CD38 expression, clinical presentation, outcome.

B-cell chronic lymphocytic leukemia (B-CLL) is the most frequent form of leukemia in Western countries; its incidence increases with age and is higher in men. B-CLL is characterized by the clonal accumulation of $CD5^+$ B-cells, with the appearance of small mature lymphocytes and a distinct immunophenotype which includes CD5, CD23, CD19 positive, weak surface Ig, and weak or negative CD22, FMC7 and CD79b.[1,2]

The clinical course of patients with B-CLL is variable. Two major staging systems are used,[3,4] together with other parameters such as lymphocyte doubling time,[5] β_2-microglobulin serum levels,[6] bone marrow histology[7] and cytogenetic abnormalities, such as deletion in 13q, deletion in 11q, trisomy of 12q, deletion in 17p, and deletion in 6q,[8-10] in order to predict the clinical course the disease.

B-CLL cells were originally considered naïve lymphocytes. Recent studies have found that the analysis of VH gene sequences can identify two B-CLL subgroups: one group of patients with somatically mutated immunoglobulin variable region genes, indicating that the B-cell has passed through the germinal center and another group of patients with unmutated sequences of VH genes, characteristic of naïve B-cells.[11-13] Continuing along this line, Damle *et al.*[14] demonstrated that CD38 expression was a surrogate marker of VH gene status: more than 30% of B-cells being $CD38^+$ was indicative of the unmutated genotype, whereas less than 30% of the B-cells being $CD38^+$ was indicative of the mutated genotype. Moreover, the group with unmutated genotype and more than 30% $CD38^+$ cells had a poor response to treatment and a shorter survival. These data were recently confirmed by Hamblin *et al.*,[15] who identified another subgroup of patients with discordant results who follow an intermediate clinical course. The prognostic value of CD38 in pre-

dicting the clinical course, progression after therapy and outcome of B-CLL patients has been reiterated by other groups.[16-19]

We report the clinical presentation and outcome of 155 consecutive patients diagnosed with B-CLL from 1991 to 1997 with a long follow-up, who were studied for CD38 expression at diagnosis. The objective of this study was to analyze whether there is an association between CD38 expression and the clinical presentation and outcome of these patients.

Design and Methods

Patients

This study was carried out in a 1,000-bed university teaching hospital in Barcelona, Spain. The hospital serves as a referral center for adults and is located in an urban area with a population of approximately one million.

From January 1991 to July 1997, peripheral blood from all patients with a suspicion of chronic lymphoproliferative disease, based on standard criteria (absolute lymphocytosis and/or abnormal lymphocytes), was systematically immunophenotyped. The antibody panel used included CD38-PE molecule. We also included in this study all consecutive patients newly diagnosed with B-CLL who attended our hematology department.

Morphologic analysis

Lymphocyte morphology was assessed on blood films stained with May-Grünwald-Giemsa. Two observers (ADC, EA) reviewed all the samples. Atypical morphology was defined as more than 10% prolymphocytes or more than 15% cells with cleaved nuclei and/or lymphoplasmacytoid cells in the blood of patients whose predominant cell type was a small lymphocyte with coarsely clumped chromatin, according to the criteria of Matutes *et al*.[20] Atypical B-CLL was only considered in those cases with the characteristic immunophenotype profile of this disease. Bone marrow biopsy was performed in 109 patients and all the biopsy samples were examined by the same pathologist (VR) and classified according to standard criteria.[7]

Clinical data

Patients were staged at diagnosis according to the Rai classification.[3] Progressive disease was defined as: lymphocyte doubling time shorter than 1 year, progression to a more advanced Rai stage, development of B-symptoms, and transformation to Richter's syndrome. Patients with progressive disease were conventionally treated with chlorambucil as first-line therapy and with fludarabine for resistant disease. Patients with stable disease were not offered chemotherapy. CLL mortality was defined as deaths related to disease progression or treatment toxicity.

Cellular immunophenotypic analysis

Immunophenotyping of all patients was performed at diagnosis with fresh peripheral blood using direct fluorescence. Cells were incubated with fluorescein isothiocyanate (FITC)-conjugated and phycoerythrin (PE)-conjugated monoclonal antibodies to the different surface molecules for 15 minutes at 25°C in a dark environment. Samples were washed twice with PBS. Erythrocytes were lysed incubating blood with FACS-lysing for 5 minutes. Negative controls consisted of cells incubated directly with FITC-conjugated and PE- conjugated isotype-matched mouse immunoglobulins. Cells were analyzed using a FACScan flow cytometer (Beckton Dickinson, San José, CA, USA) and by setting gates on lymphocyte populations based on SSC/FSC (LeucoGATE). The protocol for B-cell chronic lymphoproliferative diseases used in all cases included the following antibody conjugates: anti-CD-19-PE, CD5-FITC, anti-CD23-PE, anti-FMC7-FITC, anti-CD38-PE, anti-CD10–FITC, anti-HLA-DR-FITC, anti-CD45-FITC, anti-CD14-PE and restriction surface light chains anti-κ-FITC and anti-λ-PE, all from Becton Dickinson except for anti-FMC7-FITC from Serotec. Double color immunofluorescence was used to analyze CD19/CD5, CD19/CD38, κ/λ. The Lysys II software system (Becton Dickinson) was used to acquire and analyze the data.

Positivity was considered when at least 20% of the neoplastic lymphocytes expressed a particular antibody, except for CD38 for which the cut-off was considered to be 30%, according to recently published data.[14] We also analyzed the CD38 cut-off set at 20% as suggested by Ibrahim *et al*.[17]

All cases in our study were scored according to the Royal Marsden scoring system for CLL[1] and all cases were CD23 and CD5 positive, and had weak or negative monotypic expression of surface Ig.

Statistical analyses

Results of the descriptive analysis are expressed as means and standard deviations (SD) for continuous data and number of cases with their proportions for qualitative data. According to the percentages of $CD5^+/CD19^+$ B-cells that co-expressed CD38, the patients were classified into two groups: those with ≥ 30% $CD38^+$ and those with < 30% $CD38^+$. Statistical differences between each group were analyzed using the χ^2 test for categorical variables and Student's t-test for continuous variables. Survival

analysis was performed at the univariate level by means of Kaplan-Meier techniques to estimate overall survival and curves were compared by the log-rank test. All variables were individually evaluated in a hazard ratio model. Variables significantly related to survival were then included in the multivariate Cox proportional hazard regression model. Results of the regression analyses were expressed as a hazard ratio (HR), with its 95% confidence interval (CI). Values of $p<0.05$ were considered to be statistically significant. All these data were also analyzed for a CD38 positivity cut-off set at ≥ 20%.

Results

Clinical and biological features

This study was done on 155 patients with B-cell CLL diagnosed in our hospital from January 1991 to July 1997, and seen at least once in our outpatient hematology clinic. Their median age at diagnosis was 68 years (range 40-92 years), and the male to female ratio was 1.5:1. The patients' characteristics are summarized in Table 1. In 124 cases (81%) lymphocyte morphology was typical. Of the 107 bone marrow biopsies performed, mixed infiltration, in 52 (49%) cases, was the most common bone marrow pattern. In 3 cases, the infiltration pattern could not be evaluated because of the poor biopsy samples. A total of 98 (64%) patients had Rai stage 0 disease at diagnosis. At the time of diagnosis, 17/139 (12%) patients had high lactate dehydrogenase (LDH) and 14/53 (26%) had a high level of β_2-microglobulin.

Twenty out of 128 (16%) patients had a doubling time shorter than one year, and 56/141 (40%) patients required treatment during the study period due to progressive disease. The median follow-up of the study group was 78 months, with a range between 1 and 129 months.

Comparison of CD38⁺ and CD38⁻ subgroups

Of the 155 patients included in this study, 30 (19%) were CD38 positive (Figure 1). As shown in Table 2, CD38 positivity identified a subgroup of CLL patients with atypical morphology (p=0.004), a diffuse bone marrow pattern (p=0.016) and aggressive disease with Rai stage ≥2 (p=0.009). Furthermore, the presence of high LDH and β2microglobulin at diagnosis correlated strongly with more than 30% CD38⁺ B-cells (p=0.024 and p=0.004, respectively), together with a higher lymphocyte count at diagnosis (p=0.021). CD38⁺ patients required treatment more frequently than did CD38⁻ patients (p=0.006). All these data remained significant when a cut-off of 20% CD38 positivity was used and no new parameters emerged as being associated with CD38 positivity (Table 2).

Table 1. Clinical characteristics of the 155 patients.

Gender (male/female)	94/61 (1.5/1)
Age	
Median	68 years
Range	40-92 years
CD38 (n=155)	
30% cut-off	
<30%	125 (81%)
≥30%	30 (19%)
20% cut-off	
<20%	116 (75%)
≥20%	39 (25%)
Morphology (n=153)	
Typical	124 (81%)
Atypical	29 (19%)
Rai stage (n=153)	
0	98 (64%)
1	21 (14%)
2	18 (12%)
3	5 (3%)
4	11 (7%)
Bone marrow pattern (n=107)	
Interstitial	37 (34%)
Mixed	52 (49%)
Diffuse	15 (14%)
Not evaluable	3 (3%)
LDH (n=139)	
< 1N	122 (88%)
≥ 1N	17 (12%)
β_2 microglobulin (n=53)	
< 1N	39 (74%)
≥ 1N	14 (26%)
Doubling time < 1 year (n=128)	20 (16%)
Treatment required (n=141)	
No	85 (60%)
Yes	56 (40%)

There were significant differences in CLL-related mortality between the two groups (Figure 2), with the median survival not reached during the follow-up period (p=0.012). When the 20% cut-off was analyzed, it continued to differentiate two groups of patients (p=0.009) (Figure 3). Furthermore, we divided the patients into two groups according to Rai stage, 0-1 and 2-4, and analyzed the impact of CD38 expression on CLL-related mortality. CD38 was only significantly associated with worse outcome in patients with Rai stage 0-1 disease (p=0.012) (Figures 4-5). When CD38 expression

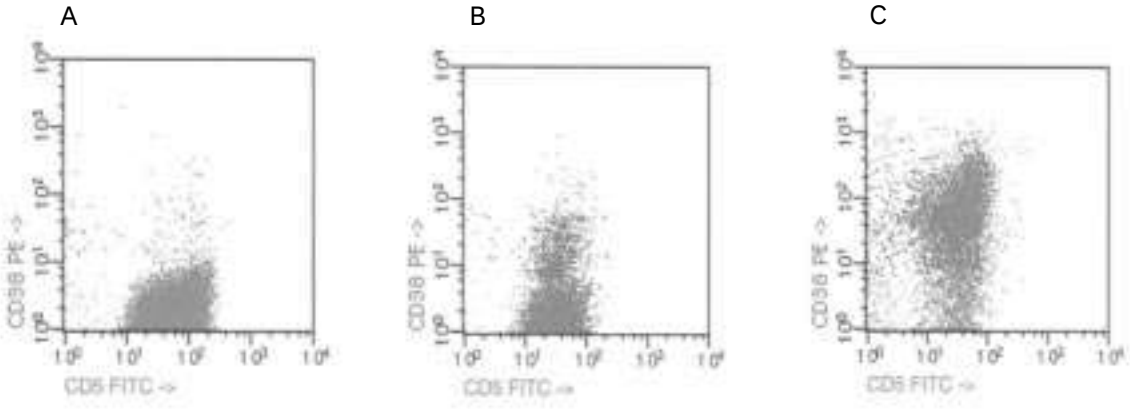

Figure 1. Representative flow cytometric profiles of CD38 expression on CD5⁺/CD19⁺ B-CLL cases. A. CD38-PE negative in CD5-FITC/CD19-PerCy5 positive cells; B. CD38 <30% in CD5-FITC/CD19-PerCy5 positive cells; C. CD38 75% in CD5-FITC/CD19-PerCy5 positive cells.

Table 2. Comparisons between CD38 positive and CD38 negative patients according to the 30% and 20% CD38 cut-offs. No major differences were found according to the two cut-offs.

	CD38 30%			*CD38 20%*		
	CD38⁺ (n=30)	*CD38⁻ (n=125)*	*p (95% CI)*	*CD38⁺ (n=39)*	*CD38⁻ (n=116)*	*p (95% CI)*
Mean age (years)	68	67.5	0.381	67	68	0.123
Gender (M/F)	18/12	76/49	0.936	26/13	68/48	0.374
Morphology						
Typical	18 (62%)	106 (85%)	0.004	25 (66%)	99 (86%)	0.006
Atypical	11 (38%)	18 (15%)		13 (34%)	16 (14%)	
Bone marrow pattern						
Diffuse	7 (32%)	8 (10%)	0.016	8 (30%)	7 (9%)	0.021
Other	15 (68%)	74 (90%)		19 (70%)	70 (91%)	
Rai stage						
0-1	18 (60%)	101 (82%)	0.009	23 (59%)	96 (84%)	0.001
2-4	12 (40%)	22 (18%)		16 (41%)	18 (16%)	
Doubling time < 1 year	5 (22%)	15 (14%)	0.356	5 (17%)	15 (15%)	0.785
High LDH (>1N)	7 (26%)	10 (9%)	0.024	10 (29%)	7 (7%)	0.002
High β_2 microglobulin (>1N)	7 (64%)	7 (17%)	0.004	7 (58%)	7 (17%)	0.008
Treatment requir.	17 (63%)	39 (34%)	0.006	21 (60%)	35 (33%)	0.005
Lymphocyte count $\times 10^9$ (mean)	18.45	12.35	0.021	30.6	18.2	0.003

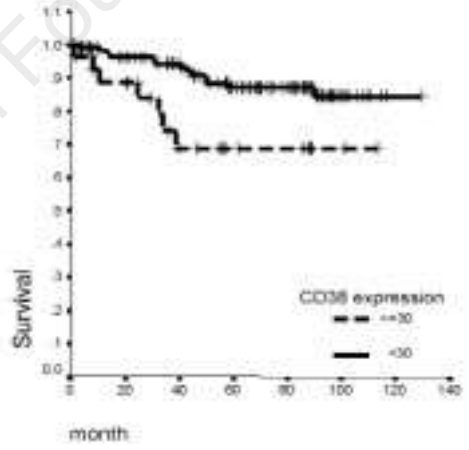

Figure 2. Kaplan-Meier CLL-related mortality curve comparing CD38 positive and CD38 negative B-CLL patients (30% cut-off). The difference is significant at *p*=0.012 (log-rank test).

was analyzed with the cut-off set at 20% it also remained a prognostic factor only for early stage patients (p= 0.009 in patients with Rai 0-1 disease vs p=0.92 in Rai stage 2-4 patients) (*curves not shown*).

Study of factors prognostic of survival

Associations between survival and the classical/known risk factors, including CD38 expression,

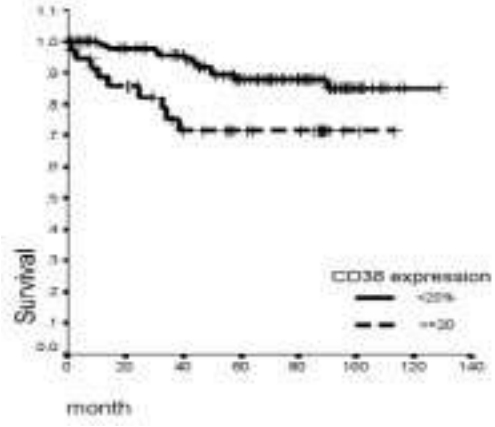

Figure 3. Kaplan-Meier CLL-related mortality curve comparing CD38 positive and CD38 negative B-CLL patients (20% cut-off). The difference is significant at *p*=0.009 (log-rank test).

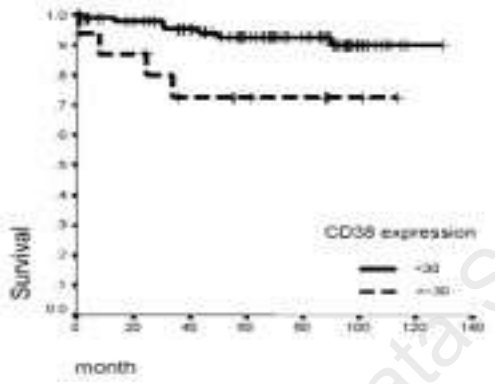

Figure 4. Kaplan-Meier CLL-related mortality curve comparing CD38 positive and CD38 negative Rai 0-1 B-CLL patients (30% cut-off). The difference is significant at *p*=0.0125 (log-rank test).

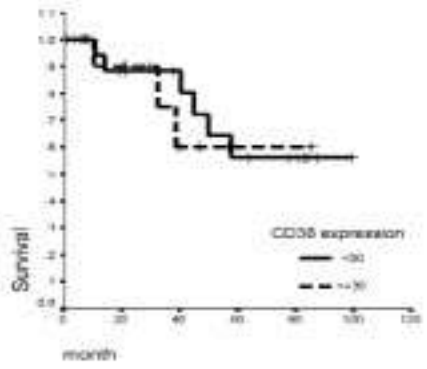

Figure 5. Kaplan-Meier CLL-related mortality curve comparing CD38 positive and CD38 negative Rai 2-4 B-CLL patients (30% cut-off). The difference is not significant *p*=0.68 (log-rank test).

Table 3. Univariate study of patients' characteristics predicting survival.

	Hazard ratio	*95% CI*	*p*
Sex	1.06	0.62-1.87	0.836
Age	1.06	1.03-1.09	<0.001
CD38 ≥ 30%	2.7	1.48-4.91	0.001
CD38 ≥ 20%	2.8	1.57-4.87	<0.001
Atypical morphology	1.6	0.85-3.03	0.144
Diffuse bone marrow pattern	4.7	2.26-9.80	<0.001
Rai stage 2-4	5.02	2.80-8.99	<0.001
Doubling time <1 year	2.5	1.22-5.09	0.012
LDH > 1N	3.8	1.84-7.84	<0.001
β_2 microglobulin >1N	6.2	2.15-18.1	0.003

Table 4. Multivariate Cox proportional hazard model on patients with all variables, except β_2 microglobulin (n=94).

	Hazard ratio	*95% CI*	*p*
Age	1.07	1.02-1.12	0.003
High LDH	3.09	1.1-8.74	0.033
Diffuse bone marrow pattern	3.41	1.2-9.5	0.019
Rai stage 2-4	5.35	2.2-13.01	<0.003
CD38 ≥ 30%	2.82	0.29-27.0	0.37
CD38 ≥ 20%	0.52	0.05-4.83	0.56

were evaluated (Table 3). Age, diffuse bone marrow pattern, Rai stage 2-4, high LDH and $\beta_2$microglobulin, doubling time < 1 year and CD38 expression (20% and 30% cut-offs) were all significant factors in determining overall survival. The prognostic factors with statistical significance were considered in a multivariate analysis (Table 4), which included 94 patients with all variables (β_2 microglobulin was excluded from the analysis due to the small number of patients who had this determination done). In this analysis, age, diffuse bone marrow pattern, Rai stage and LDH were the variables strongly associated with survival. CD38 expression, either 20% or 30% cut-off, was not a statistically significant prognostic factor.

Discussion

We report on a large number of unselected consecutive B-CLL patients studied for CD38 expression at diagnosis. In our study, CD38 identified two groups of B-CLL patients with different clinical presentations and outcomes.

As first described by Damle *et al.*,[14] CD38 expression and Ig VH gene mutations are reliable prognostic indicators of clinical course and outcome in B-CLL. This study identified 2 subsets of patients: those with >30% CD38+ lymphocytes and unmutated VH genes, characteristic of B-cells that have not entered a germinal center (GC), and those with <30% CD38+ lymphocytes and mutated V genes, characteristic of post-GC, memory B-cells. Moreover, those patients with unmutated V genes and >30% CD38+ lymphocytes had a worse clinical course and shorter survival. Data reported by Hamblin *et al.*[16] demonstrated that CD38 expression and Ig VH gene mutation were independent prognostic factors in B-CLL, although an association between both parameters was not always found. Recent data published by this group[15] report discordant results of CD38 expression and Ig VH mutations in 28% of the patients included in the analysis. This subgroup of patients follows an intermediate clinical course, with a median survival of 15 years. Other studies reported by Ibrahim *et al*.[17] and Del Poeta *et al*.,[18] reiterate the importance of CD38 expression in B-CLL as a prognostic factor in large series of patients. It is worth noting that the CD38 expression cut-off used by Ibrahim *et al*. was 20%, in contrast to the 30% cut-off used by other authors. Moreover, recently Morabito *et al*.[19] demonstrated the importance of CD38 expression in predicting progression-free survival after first-line therapy with high-dose chlorambucil.

In this study, we confirm the association between CD38 expression and most of the known bad prognostic parameters for B-CLL, such as atypical morphology, diffuse bone marrow pattern, Rai stage 2-4, high $\beta_2$microglobulin and LDH levels, as well as a higher lymphocyte count and treatment requirement. Furthermore, CD38 expression identified a subset of patients with a significantly shorter survival (p=0.012). When we divided patients into 2 groups according to their Rai stage (0-1 vs. 2-4), CD38 positivity remained significantly associated with CLL-related mortality only in the early stage group. In the multivariate analysis, age, diffuse bone marrow pattern, Rai stage 2-4 and high LDH levels were found to be independent factors predicting survival, and CD38 expression lost its statistical significance.

The results of our multivariate analysis do not corroborate those recently reported by other authors. In the study by Ibrahim *et al*.,[17] the cut-off for CD38 expression was arbitrarily set at 20%, differing from the cut-off used by Damle *et al*.[14] who reported an inverse relationship between CD38 expression (cut-off 30%) and V gene mutation status. This makes it difficult to compare results from Ibrahim's study with results from our study and for that reason we also analyzed our group of patients using a 20% cut-off for CD38 positivity. No differences were found in the univariate or multivariate analysis, or in the CLL-related mortality curves, and CD38 continued to lose its significance as an independent prognostic factor.

Del Poeta *et al.*,[18] using the same 30% cut-off for CD38 expression, only included biological variables and modified Rai stages in multivariate analysis. In our analysis we also included those biological and clinical parameters with significance at the univariate level, excluding β_2-microglobulin because of the small number of patients in whom this was measured at diagnosis.

Nevertheless, we think that CD38 evaluation is a measurable biological parameter that is not as subjective as the evaluation of some clinical parameters and which, performed at diagnosis, can identify two subgroups of B-CLL patients. Probably, biological parameters such as CD38 expression might permit other invasive prognostic proceedings included in the current staging of B-CLL to be replaced in these patients.

At present, all these data suggest that there are 2 types of B-CLL with different stages of cell origin differentiation, which might explain the clinical variability and survival seen in this disease. The study of CD38 expression in immunophenotyping protocols of B-CLL, measured under the same conditions (CD38-PE) and with a unified criterion for positivity (20% or 30%), is an interlaboratory reproducible technology that will enable the uniform study of larger series of patients. This will help in determining the exact prognostic value of CD38 in staging systems of B-CLL.

Contributions and Acknowledgments

EDD: data collection, analysis, interpretation and drafting of the article. ADC: conception, design, interpretation and final aproval of the version. EGB: interpretation of data and revising the manuscript. DB: data collection. EA: CD38 analysis. VR: interpretation of bone marrow trephines. SS, JP and AG: critical revising of the manuscript. AFS: critical revising and final approval of the article. ADC, EA: responsible for Figure 1; EDD: responsible for Figures 2-5; ADC, EDD: responsible for Tables 1-2; EDD: responsible for Tables 3-4.

We would like to thank Maite Encuentra for performing the statistical calculations.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Funding

This study was supported in part by grants from the Fundació "August Pi i Sunyer" and by FIJC-01/P-AG from the Fundació "Josep Carreras".

References

1. Matutes E, Owusu-Ankomah K, Morilla R, Garcia Marco J, Houlihan A, Que TH, et al. The immunological profile of B-cell disorders and proposal system for the diagnosis of CLL. Leukemia 1994; 8:1640-5.
2. Moreau EJ, Matutes E, A'Hern RP, Morilla AM, Morilla RM, Owusu-Ankomah KA, et al. Improvement of the chronic lymphocytic leukemia scoring system with monoclonal antibody SN8 (CD79b). Am J Clin Pathol 1997; 108:378-82.
3. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975; 46:219-34.
4. Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, et al. A new prognostic classification of chronic lymphocytic leukemia derived from multivariate survival analysis. Cancer 1981; 48:198-206.
5. Montserrat E, Sanchez-Bisono J, Vinolas N, Rozman C. Lymphocyte doubling time in chronic lymphocytic leukaemia; analysis of its prognostic significance. Br J Haematol 1986; 62:567-75.
6. Di Giovanni S, Valentini G, Carducci P, Giallonardo P. β_2-microglobulin is a reliable tumor marker in chronic lymphocytic leukemia. Acta Haematol 1989; 81:181-5.
7. Rozman C, Montserrat E, Rodriguez-Fernandez JM, Ayats R, Vallespi T, Parody R, et al. Bone marrow histologic pattern the best single prognostic parameter in chronic lymphocytic leukemia; a multivariate survival analysis of 329 cases. Blood 1984; 64:642-8.
8. Juliusson G, Oscier DG, Fitchett M, Ross FM, Stockdill G, Mackie MJ, et al. Prognostic subgroups in B-cell chronic lymphocytic leukemia defined by specific chromosomal abnormalities. N Engl J Med 1990; 323:720-4.
9. Matutes E, Oscier D, Garcia-Marco J, Ellis J, Copplestone A, Gillingham R, et al. Trisomy 12 defines a group of CLL with atypical morphology: correlation between cytogenetic, clinical and laboratory features in 544 patients. Br J Haematol 1996; 92:382-8.
10. Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000; 343: 1910-6.
11. Fais F, Ghiotto F, Hashimoto S, Sellars B, Valetto A, Allen SL, et al. Chronic lymphocytic leukemia B cells express restricted sets of mutated and unmutated antigen receptors. J. Clin Invest 1998; 102:1515-25.
12. Naylor M, Capra JD. Mutational status of Ig VH genes provides clinically valuable information in B-cell chronic lymphocytic leukemia. Blood 1999; 94:1837-9.
13. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig VH genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999; 94:848-54.
14. Damle RN, Wasil T, Fais F, Ghiotto F, Valetto A, Allen SL, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999; 94:1840-7.
15. Hamblin TJ, Orchard JA, Ibbotson RE, Davis Z, Thomas PW, Stevenson FK, et al. CD38 expression and immunoglobulin variable region mutations are independent prognostic variables in chronic lymphocytic leukemia, but CD38 expression may vary during the course of the disease. Blood 2002; 99:1023-9.
16. Hamblin TJ, Orchard JA, Gardiner A, Oscier DG, Davis Z, Stevenson FK. Immunoglobulin V genes and CD38 expression in CLL. Blood 2000; 95:2455-7.
17. Ibrahim S, Keating M, Do KA, O'Brien S, Huh YO, Jilani I, et al. CD38 expression as an important prognostic factor in B-cell chronic lymphocytic leukemia. Blood 2001; 98:181-6.
18. Del Poeta G, Maurillo L, Venditti A, Buccisano F, Epiceno AM, Capelli G, et al. Clinical significance of CD38 expression in chronic lymphocytic leukemia. Blood 2001; 98:2633-39.
19. Morabito F, Mangiola M, Stelitano C, Deaglio S, Callea V, Malavasi F. Peripheral blood CD38 expression predicts time to progression in B-cell chronic lymphocytic leukemia after first-line therapy with high-dose chlorambucil. Haematologica 2002; 87:217-8.
20. Oscier DG, Matutes E, Copplestone A, Pickering RM, Chapman R, Gillingham R, et al. Atypical lymphocyte morphology: an adverse prognostic factor for disease progression in stage A CLL independent of trisomy 12. Br J Haematol 1997; 98:934-9.

Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Estella Matutes, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Matutes and the Editors. Manuscript received April 19, 2002; accepted August 5, 2002.

What is already known on this topic

Over the last two years, a number of studies have shown the prognostic value of CD38 in CLL for disease progression and survival.

What this study adds

The present study shows that CD38 expression is associated with other poor prognostic variables in CLL. However, CD38 is only a prognostic factor for survival in early stages and in a univariate analysis.

Potential implications for clinical practice

The feasible assessment of CD38 makes it an important parameter to investigate in the routine practice as an indicator of disease outcome in CLL.

Estella Matutes, Associate Editor
(London, United Kingdom)