Absolute Lymphocyte Count with Extreme Hyperleukocytosis Does Not Have a Prognostic Impact in Chronic Lymphocytic Leukemia

LEV SHVIDEL[1], OSNAT BAIREY[2], TAMAR TADMOR[3], ANDREI BRAESTER[4], ROSA RUCHLEMER[5], RIVA FINEMAN[6], EREL JOFFE[2], ALAIN BERREBI[1], and AARON POLLIACK[7], ON BEHALF OF THE ISRAELI CLL STUDY GROUP

[1]*Kaplan Medical Center, Rehovot, Israel;*
[2]*Rabin Medical Center, Petah-Tikva, Israel;*
[3]*Bnai Zion Medical Center, Haifa, Israel;*
[4]*Western Galilee Hospital, Naharyia, Israel;*
[5]*Shaare Zedek Medical Center, Jerusalem, Israel;*
[6]*Rambam Medical Center, Haifa, Israel;*
[7]*Hebrew University Medical School, Jerusalem, Israel*

Abstract. *Background/ Aim: The prognostic significance of hyperleukocytosis in chronic lymphocytic leukemia (CLL) remains uncertain. The aim of the present study was to evaluate the clinical characteristics and outcome of patients with CLL and white blood count (WBC) >150×10⁶/l at the time of diagnosis. Patients and Methods: Using the database of the Israeli CLL Study Group, which includes 1,507 cases, we identified 41 patients diagnosed with WBC >150×10⁶/l and analyzed the survival in the group that was 62 months compared to 174 months in patients without hyperleukocytosis (p<0.001). However, multivariate analysis demonstrated that the WBC count had no predictive value in relation to survival time. While in the entire patient cohort advanced age and Binet stage, presence of thrombocytopenia and ZAP-70 expression were independently associated with poor prognosis, these parameters lost their prognostic value in patients with hyperleukocytosis. Conclusion: Although our results do not confirm that high initial levels of WBC are independently associated with shorter survival in CLL, the clinical course in these cases appears to be aggressive and conventional prognostic factors are not valid in this patient sub-group.*

Correspondence to: Lev Shvidel, Hematology Institute, Kaplan Medical Center, Rehovot 76100, Israel. Tel: +97289441383; Fax: +97289441706; e-mail: levsh@clalit.org.il

Key Words: Chronic lymphocytic leukemia, hyperleukocytosis, prognosis, survival.

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder with a variable outcome. Clinical staging systems proposed by Rai and Binet for CLL (1, 2) established anemia and thrombocytopenia as predictors of worse outcome in patients with CLL. It is of interest that although the circulating white blood count (WBC) reflects the tumor burden in individual patients with CLL, this parameter is not included in the different clinical staging classifications and its prognostic importance remains controversial. Furthermore, there are no formal recommendations relating to what absolute lymphocyte threshold should be used as a prognostic parameter in CLL as well as a guide, for when to initiate treatment in these patients. Some studies comparing patients with WBC count above or below 25 to 60×10⁹/l showed that higher counts predicted for a worse outcome (3-8), whereas other investigators reported contradictory results (9, 10). The clinical characteristics, prognosis and management of CLL patients presenting with very high to extreme lymphocytosis have still not been clearly defined. Such patients have been reported as rare or interesting individual cases associated with symptomatic leukostasis and hyperviscosity, or at the most documented in small patient cohort series. The purpose of this retrospective study was to describe the clinical characteristics and outcome of patients with hyperleukocytosis >150×10⁶/l at the time of CLL diagnosis and to summarize our experience on their management.

Patients and Methods

For the present analysis we used the database of the Israeli CLL study group (ICLLSG) that currently includes data on 1,740 patients; 1,507 of these cases were diagnosed after January 1990

based on flow cytometry results. The enrolled patients were sequentially diagnosed and relevant data was recorded in the institutional databases of eight hematology departments participating in the ICLLSG. The diagnosis of CLL was established according to the criteria of the National Cancer Institute-sponsored Working Group on CLL, as well as by their characteristic morphology and appropriate immunophenotype showing positive expression for CD19, CD5 and CD23 (11). The date of immunophenotyping had been taken as the date of CLL diagnosis. Because of the the retrospective nature of the study and the lack of accurate data obtained from local treating physicians relating to systematic follow up of WBC counts, precise analysis of cases with fluctuating WBC count was not possible; thus, as a result, only patients with leukocytosis >150×10^6 /l at time of CLL diagnosis were included in this study.

Herein, we identified 41 consecutive patients diagnosed with initial hyperleukocytosis between January 1990 and May 2014; these cases were analyzed separately. Data were collected from the medical records regarding age, gender, Binet stage, presence of lymphadenopathy and splenomegaly, WBC count, hemoglobin (Hb) and platelet level, expression of CD38 and ZAP-70 by flow cytometry, beta 2-microglobulin (b2m), IgG, IgA and IgM immunoglobulin levels, direct antiglobulin test (DAT), presence of paraproteinemia and cytogenetics by fluorescence *in situ* hybridization (FISH) at time of diagnosis. We evaluated separately the relationship between all the above factors and time to first treatment (TTT) and overall survival (OS). Data were analyzed after obtaining approval by all the individual institutes' Helsinki ethics committees.

Statistical analysis. Continuous variables and categorical variables between groups were compared using analysis of variance (ANOVA) and the Chi square test, respectively. OS was defined as the time interval from diagnosis to death due to any cause or censoring; TTT was defined as the time from diagnosis to the start of treatment for CLL or censoring. Survival curves were calculated using the Kaplan-Meier method. The log-rank test was used for statistical comparisons. Statistical significance was set at a 5% threshold. All analyses were performed using the SAS software (SAS Inc., Chicago, IL, USA).

Results

Patients' characteristics. Final analysis was performed on 1,507 CLL patients, 41 patients of them were identified with initial leukocytosis >150×10^6/l; the clinical characteristics of all patients are presented in Table I. The cohort with hyperleukocytosis represented 2.7% of all CLL patients diagnosed in this period. There were 23 males (56.1%) and 18 females (43.9%). Median age at diagnosis was 68 years (range, 49 to 89); 24 (58.5%) patients were >65 years old. All cases had typical CLL based on immunophenotyping positive for CD5 and CD19, while 36 of these cases had strong and 5 moderate expression of CD23 antigen. Ten patients (24.4%) had Binet stage A, 16 (39%) stage B and 15 cases (36.6%) were in Binet C. Three patients had autoimmune hemolytic anemia (AIHA) at the time of diagnosis, one immune thrombocytopenia and positive DAT (Evans syndrome) and 13 others had positive DAT without laboratory signs of hemolysis. Most evaluated patients had raised serum levels of b2m (30 out of 31, 96.8%) and lactate dehydrogenase (LDH) (21 out of 38, 55.3%). Serum immunoglobulin and protein electrophoresis were recorded in 31 patients; hypo-IgG (normal IgG 700-1,600 mg/dl) was seen in 10 (32.3%), hypo-IgA (normal IgA 70-400 mg/dl) in 6 (19.4%) and hypo-IgM (normal IgM 40-230 mg/dl) in 21 patients (67.8%); paraproteinemia was diagnosed in 7 patients (22.6%). Expression of ZAP-70 in >20% cells and CD38 in >30% cells were found in 21 out of 28 (75%) and 10 of 35 cases (28.6%), respectively.

No patients showed clinical signs of leukostasis, hyperviscosity or coagulation abnormalities at diagnosis. Median serum creatinine was 0.97 mg/ dl (range 0.49-1.3; normal 0.7-1.2) and median serum uric acid was 6.1 mg/dl (range 3.9-8.6, normal 2.5-7.0). There were no cases with clinically significant electrolyte abnormalities, hyperuricemia, renal failure or spontaneous tumor lysis. Management of patients with hyperleukocytosis was standard using premedication with fluids and allopurinol.

FISH analysis was mostly performed in younger patients and revealed a high rate of prognostic unfavorable genomic aberrations: 11q del (n=4), 17p del (n=3), trisomy 12 (n=2), while only one had a sole 13q del. In 6 cases no abnormalities were found.

Very high WBC at diagnosis was associated with higher prevalence of lymphadenopathy and spleen involvement, anemia, thrombocytopenia, higher Binet scores, and increased b2m levels as well as ZAP-70 expression (Table I). The pattern of cytogenetic abnormalities by FISH was comparable but results were available for only 15% (n=243) of selected cases.

Follow-up. The median follow-up time was 46 months (range 1-286 months). All but one patients (97.6%) progressed during the follow-up; 38 out of 40 (95%) patients with progressive CLL received cytoreductive treatment, and 2 patients were not treated with chemotherapy because of advanced age (80 and 89 years). The median time from CLL diagnosis to first treatment was 2 months (range=0-54). Three patients reached a WBC count of 500×10^9/l during follow-up and one developed Richter syndrome, a Hodgkin's variant. Two patients who had had positive DAT at diagnosis developed AIHA later during follow-up and 3 other patients developed AIHA shortly after starting fludarabine-containing chemotherapy; the overall prevalence of AIHA was 19.5% (8 cases).

Two thromboembolic complications were seen soon after the treatment: one patient developed deep vein thrombosis and another, who had received monthly intravenous immunoglobulin, developed bilateral pulmonary embolism. Screening for thrombophilia was performed in these patients and reported as within normal limits in all cases.

Time to treatment. Age (p=0.756), gender (p=0.493), Binet stage (p=0.518), presence of lymphadenopathy (p=0.677) and splenomegaly (p=0.45) at diagnosis did not influence the time to first treatment. Anemia with Hb <10 mg/dl (p=0.21) and thrombocytopenia <100×10^9/l (p=0.93), as well positive DAT (p=0.846) also did not predict for shorter TTT. There was no significant difference in TTT between patients with expression of CD38 and ZAP-70 and those without (p=0.469 and p=0.211, respectively). Serum b2m >normal or 2× upper normal limits (p=0.228 and p =0.081), hypo-IgG (p=0.889), hypo-IgA (p=0.9) and presence of paraproteinemia (p=0.124) did not impact the TTT, however patients with hypo-IgM values had shorter TTT (p=0.013). FISH analysis was performed in 16 selected patients; 7 cases with 17p del and 11q del had comparable TTT and were not different from those 9 showing other results (p=0.93).

Chemotherapy regimens varied over the years according to the policy of the different Departments of Hematology. First-line regimens were: oral chlorambucil with or without prednisone (n=18), cyclophosphamide, oncovine, prednisone with or without doxorubicin (COP/CHOP) (n=8), fludarabine and cyclophosphamide (FC) (n=4), fludarabine, cyclophosphamide, and rituximab (FCR) (n=7) or bendamustine and rituximab (n=1). Response was achieved in 20 patients (52.6%), complete remission in 3 and partial remission in 17. Median response lasted 12 months (range=6-20 months). Second-line treatment was given to 26 patients, while 15 required three lines of therapy or more.

Overall survival. Regarding last follow-up date, 30 patients with initial hyperleukocytosis have died; all but one from CLL and related complications. The cause of death for one elderly patient was considered as cardiovascular disease. The estimated median overall survival was 62 months (95% coincidence interval (CI)=36-88 months), while in patients without hyperleukocytosis was 174 months (95% CI=150-197 months) (p<0.001).

For stage A patients, the median survival was 62 months (95% CI=12-112); for stage B patients 74 months (95% CI=0-187); for stage C patients 43 months (95% CI=26-59). Clinical stage according to Binet did not predict overall survival (p=0.1). Age >65 years did not influence the survival in this group of patients (p=0.301). There were only 3 patients younger than 65 years with stage A CLL; one of them died 22 months after diagnosis and two are still alive at 17 and 66 months, respectively. Females had significantly inferior overall survival than males (p=0.014), which may be related to the younger median age of males (60 years and only one >80 years) compared to a median age of 69 years (and 7 elderly) for females. Presence of lymphadenopathy or splenomegaly at diagnosis did not correlate with overall survival (p=0.294 and p=0.403, respectively). Elevated serum b2m (normal, 1.8 mg/L), b2m above 2× upper normal limits and expression of CD38 and ZAP-70 did not predict shorter overall survival (p=0.414; 0.279; 0.862 and 0.22, respectively). Presence of 17p del or 11q del compared with FISH findings (no aberrations, 13q del or trisomy 12) also were not significant in terms of overall survival (p=0.104).

There was no association between serum IgG and IgA levels and overall survival (p=0.313 and p=0.27, respectively); however, low IgM values appeared to correlate with shorter survival times (p=0.01). Patients with or without paraproteinemia had comparable survival (p=0.112). There was no difference in survival between patients presenting with WBC <200×10^9/l and those with a higher WBC (p=0.756). There was a trend for better survival in patients with initial Hb levels >10 g/dl (p=0.05) and no difference with platelet count more >100×10^9/l or less (p=0.964). Positive DAT at diagnosis did not affect survival time (p=0.311); however, three patients with active AIHA had a short survival of 4, 13 and 13 months, respectively. Although no improvement in survival was seen in patients receiving FCR regimen compared with other treatments (p=0.623), the small number of treated patients preclude a valid analysis. Multivariate analysis did not reveal any variable with prognostic power relating to survival rates in this cohort of patients.

The median survival in the whole series of 1,507 CLL patients was 170 months (95% CI=148-191 months). According to multivariate analysis, age >65 years (p=0.21; 95% HR=1.9), advanced Binet stage (p=0.022; 95% HR=0.12), presence of thrombocytopenia (p=0.003; 95% HR=0.08) and ZAP-70 expression (p<0.001; 95% HR=2.99) were independently associated with shorter survival.

Discussion

In the present study, we report retrospective data obtained from a large cohort of Israeli patients with CLL and demonstrated that patients presenting with hyperleukocytosis generally have a progressive clinical course and worse prognosis independent of their clinical stage. Although hyperleukocytosis is an obvious reflection of the tumor burden in CLL, it is not considered a prognostic parameter in CLL and does not necessarily dictate treatment decisions.

In an earlier publication we reported the clinical outcome of a cohort of 1,325 patients enrolled in our CLL database (12). The median survival for Binet stage A patients was 12.2 years, for stage B was 8.5 years and for stage C was 6.4 years. Older age, advanced Binet stage, high b2m level and expression of ZAP-70, but not lymphocytosis >100×10^9/l, predicted shorter survival. Here we empirically chose a higher cut-off of WBC 15010^9/l preserving enough cases for statistical analysis and, again, could not show that initial very high WBC counts independently influence survival in CLL.

Several earlier studies have examined the prognostic value of the WBC counts in CLL with controversial results. In

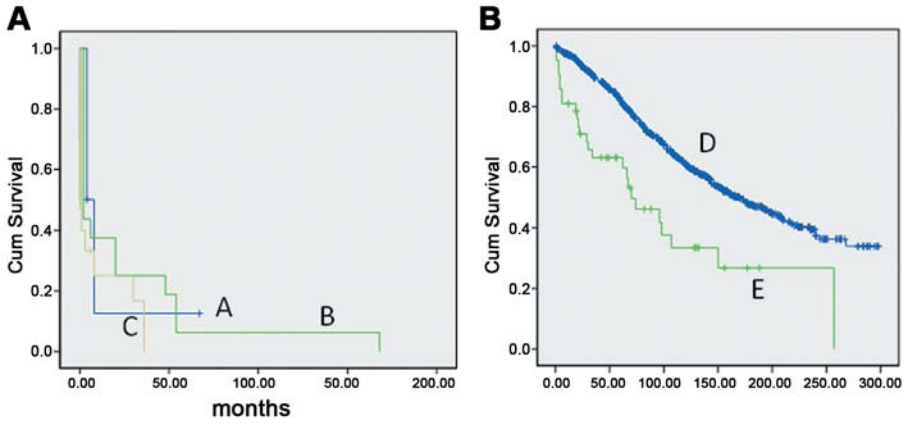

Figure 1. *(A) Overall survival curves of 41 CLL patients with initial hyperleukocytosis according to Binet stage A, B or C. (B) Overall survival curves without hyperleukocytosis (D) and with hyperleukocytosis (E).*

Table I. *Clinical and laboratory characteristics of CLL patients.*

Characteristics	WBC <150×10^9/l; n=1466	WBC >150×10^9/l;	*p*-Value n=41
Median age	68.0	67.9	0.94
Gender (male)	850 (58%)	23 (56.1%)	0.1
Lymphadenopathy	488 (33.3%)	28 (68.3%)	<0.001
Splenomegaly	299 (20.4%)	26 (63.4%)	<0.001
Anemia Hb <10g/l	83 (5.7%)	13 (31.8%)	<0.001
Thrombocytopenia <100×10^9/l	69 (4.7%)	7 (17.1%)	<0.001
Binet stage			
A	1108 (75.6%)	10 (24.4%)	<0.001
B	260 (17.7%)	16 (39.0%)	
C	98 (6.7%)	15 (36.6%)	
b2m >1.9 mg/l	426/847 (50.3%)	30/31 (96.8%)	<0.001
CD38 >30%	231/985 (23.5%)	10/35 (28.6%)	0.29
ZAP-70 >20%	117/382 (30.6%)	21/28 (75%)	<0.001

b2m, Beta 2-microglobulin

1987, the MD Anderson Cancer Center (MDACC) group reported that CLL patients with WBC <25×10^9/l had a median survival of 9.0 years compared to 3.7 years for those with counts >50×10^9/l (13). However, multivariate regression analysis showed that only uric acid, alkaline phosphatase, LDH, peripheral lymphadenopathy and age contributed to survival prediction in these patients. On the other hand, in the same year, an Italian group evaluated 1,985 untreated patients and showed that peripheral blood lymphocyte count had an independent impact on survival (3). In a more recent report, Italian investigators also showed that the WBC count at diagnosis along with immunoglobulin gene mutations are the only independent predictors of treatment-free survival in young patients with stage A CLL (4). In a prospective French study performed to validate the prognostic impact of routine parameters, lymphocytosis emerged as one of the 4 independent factors predicting survival for Binet stage A patients (5). Later, in 2010, in a large retrospective cohort of more than 2,000 patients followed for a period of 20 years, the MDACC group identified lymphocytosis >30×10^9 /l as an independent predictor of shorter survival (6). However, it should be noted that other studies relating to the degree of peripheral blood leukocytosis and shorter overall or progression-free survival, have yielded conflicting results (7-10).

Different WBC cut-off values as a prognostic indicator in CLL have been explored; however, only a few studies dealt with the frequency of hyperleukocytosis and its clinical and prognostic significance in CLL. In 2002, Silverman *et al.* reported that the development of leukocytosis >100×10^9/l during the course of CLL did not predict for shorter overall survival (14). The median overall survival for the 82 patients who had never developed a WBC count greater than 100×10^9/l was 101 months compared to 107 months for 41 patients who had at least one event of hyperleukocytosis. However, median survival for these patients, after the first occurrence of hyperleukocytosis, was only 40 months.

De Torres and Hernandez compared two groups of CLL patients with and without leukocytosis of 100×10^9/L (15); 10 out of 93 patients (10.8%) had hyperleukocytosis. However, both groups had similar demographic, clinical, immunophenotypic and cytogenetic profiles and the only difference seen was in the platelet counts.

In general, symptomatic hyperleukocytosis is more common in acute leukemias (16) but several reports have concentrated on cases of CLL presenting with symptoms related to leukostasis. In CLL, cellular hyperviscosity and

leukostasis (caused by the formation of WBC aggregates and thrombi) are rare complications, probably due to the small size of circulating lymphocytes and their rheological characteristics, which are very different from those of neutrophils. Occasionally, cases of CLL with extreme hyperleukocytosis $>1000\times10^9$/l have been reported to develop neurological abnormalities, retinal hemorrhages, lung infiltrates or thrombosis (17-19).

Baer *et al*. described 16 patients with WBC counts of 500 to $1{,}700\times10^6$/l, (10 males and 6 females with a mean age of 60 years) (17). Five of them had hyperleukocytosis early in the course of their disease while 11 developed this abnormality at a late stage. Three of these cases had clinical signs of hyperviscosity but no features predictive of the occurrence of hyperviscosity syndrome were identified.

Similar to Silverman *et al*. (14) who observed 6% patients with leukocytosis $>100\times10^9$/l, we also found only a small proportion of patients with high WBC counts at diagnosis. During the time period 1990 to 2014, we identified 41 CLL patients with hyperleukocytosis $>150\times10^9$/l at diagnosis (2.7% of all patients diagnosed in this period). The median survival in this cohort was 62 months, approximating survival times for all stage C in the whole series. Almost all patients with hyperleukocytosis had a progressive course with short TTT and required cytoreduction. It is of interest that median survival in these patients was not associated with Binet stage at all. In addition, all other well recognized prognostic features did not correlate with overall survival or TTT and the only variable with an adverse outcome in univariate analysis was the presence of decreased levels of IgM, which may even represent a bias considering the small cohort of patients included.

It is also of interest that none of the patients included in the present study had significant symptoms of leukostasis, renal impairment or electrolyte disturbances; however, two developed a thrombotic complication following treatment. In this respect, it is also noteworthy that Whittle *et al*. reported incidence rates of 1.45% per patient year, for venous thromboembolism in an unselected UK CLL clinic population, which is ten-fold higher that the incidence estimated in the general population (20). Another interesting finding relates to the high prevalence of 20% for AIHA, which is consistent with previous reports by Mauro *et al*. and Moreno *et al*. showing that the occurrence of AIHA is associated with a higher lymphocyte count (21, 22).

In conclusion, in this study we showed that, although CLL patients presenting with hyperleukocytosis at diagnosis generally have an aggressive clinical course, this is not an independent predictor of survival in CLL. It is of interest that Binet stage and other well-recognized prognostic characteristics in CLL were not valid in this sub-group of patients. No cases of hyperviscosity or leukostasis were seen in the examined patient cohort.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

References

1 Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN and Pasternack BS: Clinical staging of chronic lymphocytic leukemia. Blood *46(2)*: 219-234, 1975.

2 Binet JL, Auquier A, Dighiero G, Dighiero G, Chastang C, Piguet H, Goasguen J, Vaugier G, Potron G, Colona P, Oberling F, Thomas M, Tchernia G, Jacquillat C, Boivin P, Lesty C, Duault MT, Monconduit M, Belabbes S and Gremy F: A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer *48(1)*: 198-206, 1981.

3 Mandelli F, De Rossi G, Mancini P, Alberti A, Cajozzo A, Grignani F, Leoni P, Liso V, Martelli M and Neri A: Prognosis in chronic lymphocytic leukemia: a retrospective multicentric study from the GIMEMA group. J Clin Oncol *5(3)*: 398-406, 1987.

4 Del Giudice I, Mauro FR, De Propris MS, Santangelo S, Marinelli M, Peragine N, Di Maio V, Nanni M, Barzotti R, Mancini F, Armiento D, Paoloni F, Guarini A and Foà R: White blood cell count at diagnosis and immunoglobulin variable region gene mutations are independent predictors of treatment-free survival in young patients with stage A chronic lymphocytic leukemia. Haematologica *96(4)*: 626-630, 2011.

5 Letestu R, Lévy V, Eclache V, Baran-Marszak F, Vaur D, Naguib D, Schischmanoff O, Katsahian S, Nguyen-Khac F, Davi F, Merle-Béral H, Troussard X and Ajchenbaum-Cymbalista F: Prognosis of Binet stage A chronic lymphocytic leukemia patients: the strength of routine parameters. Blood *116(22)*: 4588-4590, 2010.

6 Tsimberidou AM, Wen S, O'Brien S, McLaughlin P, Wierda WG, Ferrajoli A, Faderl S, Manning J, Lerner S, Mai CV, Rodriguez AM, Hess M, Do KA, Freireich EJ, Kantarjian HM, Medeiros LJ and Keating MJ: Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. J Clin Oncol *25(20)*: 4648-4656, 2007.

7 Rozman C, Montserrat E, Felíu E, Grañena A, Marín P, Nomdedeu B and Vives Corrons JL: Prognosis of chronic lymphocytic leukemia: a multivariate survival analysis of 150 cases. Blood *59(5)*: 1001-1005, 1989.

8 Kröber A, Seiler T, Benner A, Bullinger L, Brückle E, Lichter P, Döhner H and Stilgenbauer S: V(H) mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood *100(4)*: 1410-1416, 2002.

9 Karmiris T, Rohatiner AZ, Love S, Carter M, Ganjoo RK, Amess J, Norton AJ and Lister TA: The management of chronic lymphocytic leukemia at a single centre over a 24-year period: prognostic factors for survival. Hematol Oncol *12(1)*: 29-39, 1994.

10 Hallek M, Wanders L, Ostwald M, Busch R, Senekowitsch R, Stern S, Schick HD, Kuhn-Hallek I and Emmerich B: Serum beta(2)-microglobulin and serum thymidine kinase are independent predictors of progression-free survival in chronic lymphocytic leukemia and immunocytoma. Leuk Lymphoma *22(5-6)*: 439-447, 1996.

11 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, Hillmen P, Keating MJ, Montserrat E, Rai KR and Kipps TJ; International Workshop on Chronic Lymphocytic Leukemia: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood *111(12)*: 5446-5456, 2008.

12 Shvidel L, Braester A, Bairey O, Rahimi-Levene N, Klepfish A, Herishanu Y, Shtalrid M, Polliack A and Berrebi A; Israeli CLL Study Group: Survival trends among 1,325 patients with chronic lymphocytic leukemia seen over the past 40 years in Israel. Am J Hematol *88(12)*: 985-992, 2011.

13 Lee JS, Dixon DO, Kantarjian HM, Keating MJ and Talpaz M: Prognosis of chronic lymphocytic leukemia: a multivariate regression analysis of 325 untreated patients. Blood *69(3)*: 929-936, 1987.

14 Silverman JA, Franssen E, Buckstein R and Imrie KR: The development of marked elevation in white blood cell count does not predict inferior outcome in chronic lymphocytic leukemia. Leuk Lymphoma *43(6)*: 1245-1251, 2002.

15 De Torres A and Hernandez A: Hyperleukocytosis and chronic lymphocytic leukemia: comparing clinical, immunophenotypic, and cytogenetic data. Cureus *4*: 503e, 2012.

16 Lichtman MA and Rowe JM: Hyperleukocytic leukemias: rheological, clinical, and therapeutic considerations. Blood *60(2)*: 279-283, 1982.

17 Baer MR, Stein RS and Dessypris EN: Chronic lymphocytic leukemia with hyperleukocytosis. The hyperviscosity syndrome. Cancer *56(12)*: 2865-2869, 1985.

18 Cukierman T, Gatt ME, Libster D, Goldschmidt N and Matzner Y: Chronic lymphocytic leukemia presenting with extreme hyperleukocytosis and thrombosis of the common femoral vein. Leuk Lymphoma 2002 *43(9)*: 1865-1868, 2002.

19 Davies CE, Whitelocke RA and Agrawal S: Retinal complications associated with hyperviscosity in chronic lymphocytic leukaemia. Intern Med J *38(2)*: 140, 2008.

20 Whittle AM, Allsup DJ and Bailey JR: Chronic lymphocytic leukaemia is a risk factor for venous thromboembolism. Leuk Res *35(3)*: 419-421, 2011.

21 Mauro FR, Foa R, Giannarelli D, Cordone I, Crescenzi S, Pescarmona E, Sala R, Cerretti R and Mandelli F: Clinical characteristics and outcome of young chronic lymphocytic leukemia patients: a single institution study of 204 cases. Blood *94(1)*: 448-454, 1999.

22 Moreno C, Hodgson K, Ferrer G, Elena M, Filella X, Pereira A, Baumann T and Montserrat E: Autoimmune cytopenias in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. Blood *116(23)*: 4771-4776, 2010.

Received January 22, 2015
Revised January 29, 2015
Accepted February 2, 2015