CHRONIC LYMPHOCYTIC LEUKEMIA IN TURKISH POPULATION: REVIEW 64 CASES

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SUMMARY: Review of 64 Turkish cases of chronic lymphocytic leukemia (CLL) has been presented in this report. 52 % of the patients were anemic; meam peripheral blood lymphocyte count was 95 X 10^9/L and 54 % of the patients had lymphocyte counts more than 50 X 10^9/L. 46% of the patients were at stage C, according to Binet's system. These results may suggest that Turkish CLL patients are younger and / or at more advanced stages than European or American patients, at the time of the diagnosis. This suggestion needs further data for confirmation. This review also confirms that Binet's method of clinical staging is more rational than Rai's method, as emphasised by many studies.

Key Words: Chronic lymphocytic leukemia, lymphocytosis, lymph node enlargement, staging.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a relatively benign lymphoproliferative disorder characterized by proliferation and accumulation of mature-appearing lymphocytes. It is the commonest leukemia in Europe and united States, but is rather rare in Asia (7). Staging of CLL had been first established by Rai *et al.* (15). During the following years, many authors proposed too many systems for staging (1,2,8,9,11,18,20). Nowadays, the staging systems defined by Rai and Binet are the two popular ones (2,15).

In this retrospective analysis, we evaluated 64 Turkish CLL patients and compared with the series in the literature.

MATERIALS AND METHODS

In this retrospective analysis, 64 CLL patients, diagnosed between January 1975 and April 1988, were evaluated. 48 were diagnosed at Hacettepe Medical School, Ankara (HMS) and 16 were diagnosed at other centers and referred because of treatment failure or patients wishes.

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The diagnosis was made mostly on the basis of peripheral lymphocytosis (more than 5x10^9/L) and infiltration of bone marrow (more than 25%) and/or lymph nodes with mature-appearing, small lymphocytes (3,14). Lymph node biopsy consistent with well-differentiated lymphocytic lymphoma plus peripheral lymphocytosis (more than 5x10^9/L) was accepted as CLL (13). In some cases, marked and sustained peripheral lymphocytosis (more than 100 x 10^9/L for more than 6 months) combined with clinical features were used to make the diagnosis. Five of the six patients, whose peripheral blood lymphocyte counts were less than 15 x 10^9/L, had lymphocytic infiltration of bone marrow (BM) and/or lymph nodes and during follow-up all succembed into classical features of CLL. The sixth one, who had not an initial biopsy, was followed for 6 years and before his death he had the full-blown clinical picture of the disease with multiple lymphadenopathies, enlargement of spleen and liver, hypogammaglobulinemia, recurrent bouts of pneumonias and urinary tract infections and severe lymphocytosis- up to 400 x10^9/L. Also, two years after the initial diagnosis, his BM biopsy showed diffuse lymphocytic infiltration. 13 patients had neither BM aspiration or biopsy nor lymph node biopsy; but all had lympocyte counts more than 40 x 10^9/L initiall, which gradually increased up to 70-400 x 10^9/L. All these patients developed the classical clinical and laboratory features of the disease during the follow-up period and without any question accepted as CLL.

Lymphosarcoma cell leukemia and prolymphocytic leukemia are excluded (19, 21). 3 cases initially diagnosed as CLL exhibited pro-lymphocytic transformation during the course of the disease and accepted as CLL/PL (Prolymphocyte / all lymphoid cells ratio on peripheral blood films between 10 and 50 %) (12). These are included.

For staging, methods of Rai and Binet were used and compared (2, 15). The limits we accepted are 5x10°/L for lymphocytosis, 11 gr/dl of hemoglobin level for anemia and 100x10°/ L for thrombocytopenia.

Table 1: AGE Distribution of Patients.

	Men	Women	Total
No. of pts.	40	24	64
Mean ± SX	58.3 ± 1.9	60.9 ± 1.9	59.3 ± 1.4
Range	35 - 80	38 - 75	35 - 80
Age	Number of patients		
Less than 40	3	2	5
40 - 49	8	-	8
50 - 59	10	6	16
60 - 69	10	11	21
70 or more	9	5	14
	NS (Not significant)		

Table 2: Initial Symptoms.

Symptom	No.	%
Periferal lymphadenopathy	20	31
Fatigue	17	27
Abdominal pain/fullness	13	20
Frequent infections	7	11
Fever	6	9
Weight loss	2	3
Easy bruising	2	3
Miscellaneous	5	7
Asymptomatic	6	9

Table 3: Initial Physical findings.

Physical findings	No.	%
LAP	48	75
SM	41	64
HM	36	56
HSM and LAP	31	48
Neither HSM nor LAP	8	12

LAP: Periperal lymphadenopathy

SM: Splenomegaly

HM: Hepatomegally, HSM: Hepatosplenomegally

Statistical analysis was performed by Student's test and X-square test. Results are expressed as mean ± standard error (SX).

Unfortunately prognostic factors and survival rate analysis could not be utilized because of the small number of the patients and short follow-up durations.

RESULTS

There were 40 men and 24 women (ratio 1.67). Mean age was 59.3 ± 1.4 (mean ± standard error), and median age was 60 (range 35-80) with no significant difference between the sexes. 80% of the patients were older than 50 (Table 1).

Table 4: Initial Hemoglobin Values.

Hb (gr/dl)	-8.0	8.0-10.9	11.0-13.9	14.0+	Total
No. of pts.	8	17	12	11	48
%	17	35	25	23	100

Table 5: Mean Periphal Lymphocyte Counts.

Stage (Rai)	Lymphocyte count (X 10^9/L)	Stage (Binet)	Lymphocyte count (X 10^9/L)
	Mean ± SX		Mean ± SX
0	30 ± 8	A	29 ± 6
1	22 ± 5		
2	54 ± 15	B	54 ± 17
3	177 ± 33		
4	126 ± 33	C	161 ± 25
Total (n=64)	95 ± 15	Stages 2 and 3 : t=3.22, p<0.01 Stages B and C : t=3.03, p<0.01 Other consequent stages : NS	

Table 6: Distribution of Patients according to Lympohoycte Counts

Lymphocyte count						
(x 10^9/L)	-15	15-50	50-100	100-300	300+	Total
No. of pts.	6	16	9	13	4	48
%	13	33	19	27	8	100

Table 7: Distribution of Lymphocyte/Total WBC Ratio.

Lymphocyte ratio (%)	50-69	70-89	90-94	95-100	Total
No. of pts.	6	19	10	13	48
%	13	39	21	27	100

Table 8: Distribution of Patients according to the Stages (Diagnosis elsewhere).

Stage (Rai)	0	1	2	3	4	Stage (Binet)	A	B	C
No. of pts.	-	1	4	3	8		1	4	11
%	-	6	25	19	50		6	25	69

Table 9: Distribution of Patients according to Age-Sex and Stages (Diagnosed at HSM).

Stage (Rai)	of pts. (%)	Men	Women	Age (Mean ± SX)
0	5(10)	3	2	61.8 ± 5.8
1	8(17)	6	2	49.9 ± 2.6
2	13(27)	7	6	64.3 ± 2.8
3	15(31)	10	5	62.3 ± 3.3
4	7(15)	4	3	57.1 ± 3.4
Stage (Binet)				
A	15(31)	7	8	59.0 ± 3.0
B	11(23)	9	2	59.9 ± 3.5
C	22(46)	14	8	60.6 ± 2.5
Total	48(100)	30	18	

Stages 0-1 (Ages) : t= 2.21, p<0.05
Stages 1-2 (Ages) : t= 3.65, p<0.01
Stages 1-3 (Ages) : t= 2.64, p<0.02

Table 10: Immunoglobulin Levels.

	IgG	IgA	IgM
Normal or increased	17	12	12
Decreased	6	11	11

Table 11: Hypogammaglobulinemia at Different Stages.

Stage (Rai)	0	1	2	3	4	Stage (Binet)	A	B	C	Total
HG + Present	-	-	5	7	3		-	5	10	15
HG absent	1	2	13	3	7		6	10	10	26
Total	1	2	18	10	10		6	15	20	41

Table 12: Types of Infections.

Infection	No. of pts
Pneumonia	19
Upper respiratory tract inf	10
Otitis media	3
Tonsillopharyngitis	7
Urinary tract infections	7
Zona zoster	5
Skin infections	4
Pseudomonas sepsis	3
Candida sepsis	2
Rectal abscess	2
Cultur negative sepsis	1
Deep cervical infection	1
Total	54

Table 13: Infections at Different Stages.

Stage (Rai)	0	1	2	3	4	Stage (Binet)	A	B	C	Total
No. of inf.	1	5	13	14	21		7	12	35	54
%	2	9	24	26	39		13	22	65	100
Inf/year/pt	.44	.56	.40	1.42	1.29		.67	.36	1.34	.78

Table 14: Hypogammaglobulinemia and Infections.

Hypogammaglobulinemia	Present	Absent	Unknown	Total
No. of infections	14	11	29	54

Table 15: Hemolytic Anemia at Different Stages.

Stage (Rai)	0	1	2	3	4	Stage (Binet)	A	B	C	Total
No. of pts.										
Coombs (+)	-	-	3	-	3		1	2	3	6
Coombs (-)	2	2	8	8	9		6	6	17	29

Table 16: Histopathologic Examinations.

46 BM aspiration smears (from 45 patients)
- 18 severe lymphocytic infiltration (lymphocyte ratio more than 90 %)
- 16 modetare lymphocytic infiltration (lymphocyte ratio : 50 - 90 %)
- 9 mild lymphocytic infiltration (lymphocyte ratio: 25 - 50 %)
- 2 dry tap (See text)
- 1 normal (See text)

26 BM biopsies
- 18 diffuse infiltration (3 increased reticulin)
- 5 nodular infiltration (1 increased reticulin)
- 1 erythroidhyperplasia + increased reticulin (See text)
- 2 normal (See text)

24 lymph node biopsies
- 22 diffuse infiltration
- 1 hyperplastic lymph node
- 1 nodular infiltration

9 other biopsies
- 4 skin biopsies (Perivascular lymphocytic infiltration, exfoliative dermatitis, zoster, lesion malignant melanoma)
- 1 liver biopsy (Periportal lymphocytic infiltration)
- 1 pleura biopsy (Diffuse lymphocytic infiltration)
- 1 nasopharynx biopsy (Diffuse lymphocytic infiltration)
- 1 lung biopsy (Interstitial fibrosis)
- 1 kidney biopsy (Renal cell carcinoma)

Table 17: BM Infiltration Patterns at Different Stages.

Stage (Rai)	0	1	2	3	4	Stage (Binet)	A	B	C	Total
Pattern										
Nodular	-	1	2	1	1		3	-	2	5 (22%)
Diffuse	2	-	6	4	6		2	6	10	18(78%)

The follow-up period ranged from 1 to 90 months. 43 cases (67%) were followed less than 12 months. Only 11 cases (17%) were followed more than two years. Mean follow-up period was 13.1 ± 2.4 months.

6 patients (9%) were asymptomatic and the diagnosis were made incidentally. The major symptom leading the patients for seeking medical aid was peripheral lymphadenopathy (Table 2).

While 48(75%) of the patients had enlarged peripheral lymph nodes at the initial physical examination, 8 (12%) had neither hepatosplenomegaly nor lymphadenopathy (Table 3).

Basic hematologic parameters of the patients are presented below, but the pattents who had been diagnosed elsewhere are not included, because all had prior chemotherapy and some had BM aplasia due to intensive chemotherapy. Furthermore, they were significantly at more advanced stages, resulting with anemia and thromboctopenia.

Of 48 cases, diagnosed at our hospital, 25 (52%) were anemic and 7(15%) were thrombocytopenic. 8 cases (17%) had severe anemia (Hb less than 8 gr/dl) (Table 4).

Mean periferal blood lymphocyte count was 95 ± 15 x 10^9/L. Lymphocyte counts showed difference between stages 0-1-2 and 3-4. Initial lymphocyte counts of 26 cases (54%) were more than 50 x10^9/L. Lymphocyte/total WBC ratio distribution is also shown (Tables 5,6,7).

The number of cases at all stages are shown at tables 8 and 9. The mean ages and sex distribution were not significantly different between the stages.

32 cases' humoral immunity status were evaluated by means of protein electrophoresis and/or immunoglobulin (Ig) levels during total 41 stages. 13 of these cases (41 %) had hypogammaglobulinemia at any stage during the course of the disease. IgA and IgM levels seemed to decline earlier than IgG. Hypogammaglobulinemia tended to occur more frequently at more advanced stages, although not significant statistically (Tables 10, 11).

30 patients developed 54 infections most of which were pneumonia, upper respiratory tract infections and urinary tract infections (Table 12). Distribution according to the stages are shown at Table 13. When these figures are corrected according to the number of patients and time values of the number of infections per year per patient were obtained for all stages. This parameter showed no increase up to Rai stage 3 and was not also different between stages 3 and 4 (Table 13). Humoral immunity status and number of infections are crossed at Table 14.

6 of 64 patient had Coombs (+) immune hemolytic anemia (Table 15).

Bone marrow aspiration was performed to 45 patients (total 46). Two aspirations were unsatisfactory (dry tap); BM biopsies of both showed diffuse lymphocytic infiltration. One patient who diagnosed and treated elsewhere

Table 18: Causes of Deaths.

Sepsis...7 (E. Coli 3, Pseudomonas 2, Candida 1, Culture negative 1)...7
Intracranial hemorrage due to thrombocytopenia.....1
Acute respiratory distress syndrome secondary to pneumonia.....1
Acuta renal failure due to hemolytic transfusion reaction.....1
Respiratory failure due to acute neuropathy (??).....1
Heart failure.....1

Table 19: Distribution of Deaths according to the Stages.

Stage (Rai)	0	1	2	3	4	Stage (Binet)	A	B	C
No of deaths	-	-	3	4	5		2	1	9

Table 20: Treatment Strategies.

Stage (Rai)	0	1	2	3	4	Stage (Binet)	A	B	C
No. of pts.									
No treatment	5	10	12	-	1		15	12	-
Chlorambucil	-	1	15	14	7		7	9	21
Steroid	-	1	2	1	1		1	2	2
Chloramb + Ste.	-	-5	1	9	-		5	10	
COP.0+PorC+p	-	-	1	9	6		-	1	15
Radiotherapy	-	-	-	2	1		-	-	3

C: Cyclophosphamide, O: Vincristine P: Priednisolon

Table 21: Progression of Disease

Stage (Rai)	0	1	2	3	4	Total	Follow-up duration (Mean ± SX)
0	2	-	3	-	-	5	7 ± 2 months
1	-	5	2	1	1	9	33 ± 5 months
2	-	-	12	4	1	17	16 ± 4 months
3	-	1	2	14	1	18	5 ± 2 months
4	-	-	-	-	15	15	10 ± 3 months
Stage (Binet)	A	B	C	Total		Follow up duration (Mean ± SX)	
A	10	3	3	16		23 ± 6 months	
B	-	11	4	15		16 ± 3 months	
C	2	1	30	33		7 ± 2 months	

Rows represent the numbers of the patients at that stage initially. Columns represent the numbers of the patients at that stage terminally.

had normal BM aspiration smear; after examining the initial BM smear, the diagnosis was confirmed and he was accepted to be in remission (Table 16).

Transiliac BM biopsies were obtained from 26 patients. BM biopsy of a patient with hemolytic anemia showed erythroid hyperplasia and increased reticulin. Two patients' biopsies were interpreted as "normal" one of whom was the patient in remission (described above), the other had 40% lymphocytes at BM smear and was considered to be possible early nodular infiltration. The distribution of the histologic BM infiltration pattern according to the stages are shown at Table 17.

9 biopsies other than BM and lymph nodes were obtained. 4 showed lymphocytic organ infiltration (Table 16).

12 of 64 patients (19%) died 20.2 $\pm$ 7.8 months after the initial diagnosis. Death rates for the patients diagnosed at our hospital and elsewhere were 6/48 (12.5%) and 6/16 (37.5%), respectively ($t= 2.219$, $p<0.05$). Death rates were 25% and 8% for men and women, respectively (Notsignificant). The causes of deaths and their distribution according to the stages are shown at Tables 18 and 19.

Lymphocyte phenotyping were obtained from 11 patients. All had B-CLL.

Therapy protocols were evaluated. At stages 0 and 1, usually no treatment were given. Daily chlorombucil (2-8 mg/day) was the mostly performed treatment for advanced stages (Table 20).

In Table 21, the numbers of patients at each stage at the time of the diagnosis and the end of the follow-up period are shown. It is easily seen that there is not significant progress during the follow-up period of each group.

DISCUSSION

The age and sex distribution of the series is in agreement with previous studies. Reported mean or median ages are between 55-68 all with no difference between sexes and stages. Men/women ratio of our series is also similar with the literature. This ratio has ben reported between 1.5 and 2.0 (1,2,6,9,10,15,16,17).

Initial physical examination findings are also consistent with previous reports (2,6,9).

Our series differs from the most others on the basis of hematalogic parameters. Although we proposed $5X10^9$/L and 25 % for limits of peripheral blood lymphocyte counts and BM infiltration with-lymphocytes, respectively, our patients initial hemoglobin levels are less, lymphocyte counts are more and they are at more advanced stages comparing with the subjects of the series with diagnostic limits described above, $15X10^9$/L and 40%.

More than half of our patients are anemic at the time of diagnosis, while this figure has been reported about 15-30 % (6,9,15).

Mean peripheral blood lymphocyte count of our series is 95 X 10^9/L and 54% of patients lymphocyte counts are more than 50 X 10^9/L. These values are usually reported about 40-70 X 10^9/L and 20-40%, respectively (2,3,6, 9,15). It has been demonstrated that lymphocyte counts increases as the stage advances, as this series reflects also (2,15).

Although sex, age and physical examination findings are similar with many series, the distribution of the patients according to the stages are quite different. In no studies compared, so low case percents for stages Rai 0 and 1 and Binet A and B, and so high case percents for stages Rai 3 and Binet C, are not reported (1,2,3,5,6, 9,10,15,17,20). This may occur because of late reference to medical care; the patients may have lived with the disease for months or even years before the initial diagnosis and when CLL had been diagnosed, they were at advanced stages. But this does not seem so rational, because CLL is known to be a slowly progressing disease, especially at the early stages (2,14,15,17). In our series, the number of patients at each stage were not different between the time of the diagnosis and the end of the follow-up period (mean 13.1 months). If late reference was the cause of this distribution pattern, then our patients mean age at the time of the diagnosis would be older; or this result may suggest that CLL may begin earlier at Turkish patients than European or American. This supposition needs further information about Turkish or Asian CLL patients.

Humoral immudeficiency and tendency to infections were seen at some of our patients. These seem to increase with progression of the disease. The most common infections in our series were pneumonia and upperrespiratory infections as expected (4,17).

18 of 23 BM biopsies (78%) which were classified as nodular or diffuse according to lymphocytic infiltration pattern, was diffuse. This is also higher than 30-50%, reported at some studies (3,6,10,16).

Although we could not study prognosis and survival rates, we intended to compare Rai and Binet's staging criteria, according to some parameters, which show tendency to differs as the stage advances. Mean peripheral lymphocyte count, hypogammaglobulinemia and fre-

quency of infections which seem to increase as the stage advances, were not different between stages O and 1 and stages 3 and 4. Mean lymphocyte counts showed significant increase between stages 2 and 3 and stages B and C, only. Other consequent stages were not different. There were not enough subjects for meaningful statistical analysis, but it is apparently seen that hypogammaglobulinemia did not increase at stage 4 with regard to stage 3. also infection rates were different only between stages 2 and 3 and stages B and C.

Although not supported by statistical results, overall, mainly because of the small number of the subject, our series exhibits, consistency with the reports that suggest that five stages are unnecessary for staging and anemia and thrombocytopenia need not to be stages as different (2,3,5).

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