

## RESEARCH ARTICLE

# Survival and Clinical Aspects for Patients with Chronic Lymphocytic Leukemia in Kermanshah, Iran

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### Abstract

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in Western countries but is relatively rare in Asia. Immune hemolytic anemia, Evan's syndrome, lymphadenopathy, organomegaly and B symptoms are the main complaints of patients in CLL. The present retrospective analysis evaluated a group of 109 patients with CLL over a 9-year period, studying correlations between sex, age and overall survival. The patients were hospitalized in the Clinic of Hematology and Oncology, Kermanshah, Iran, between 2006 and 2014. Data analysis for sex and age was performed using IBM SPSS19 and overall survival was plotted by Kaplan-Meier plot, Log-rank test in Graph Pad prism 5 Software for five-year periods. The mean age of diagnosis for CLL patients was 60.73 years, 59.6% male. Survival rate patients was 64% and mean overall survival was 38.5 months. In the Rai system, fourteen patients (12.8%) had stage III and twenty eight patients (25.7%) had stage IV. Most frequent clinical features in patients with CLL were lymphadenopathy (38.7%) and organomegaly (34%), respectively. There is not relationship between sex and age in patients but overall survival rate in females was higher than in males. In Asian countries, CLL is more in male and in age above 60 years. Complaints about lymphadenopathy and virus infection are prevalent.

**Keywords:** Chronic lymphocytic leukemia - age - sex - survival - Kermanshah, Iran

*Asian Pac J Cancer Prev*, 16 (17), 7987-7990

### Introduction

Chronic lymphocytic leukemia (CLL) is associated with a state of immunosuppression characterized by hypogammaglobulinemia as well as B and T lymphocyte dysfunction (Sarkar et al., 2014).

CLL is a disease of the elderly, yet few clinical trials include a significant number of older patients, and outcomes after specific therapies can be different depending on age (Woyach et al., 2013). The median survival for all patients with CLL is widely variable and, depending on prognostic factors, ranges from 18 months to greater than 10 years (Siddon et al., 2013), but overall survival is worse in older patients (Stephens et al., 2012).

Staging is useful in CLL to predict prognosis and also to stratify patients to achieve comparisons for interpreting specific treatment results. Anemia and thrombocytopenia are the major adverse prognostic variables. CLL has no standard staging system. The Rai staging system has from stage 0 to IV and the Binet classification has stage A, stage B and stage C (Rai et al, 1975; Binet et al, 1981).

Autoimmune hemolytic anemia (AIHA) is the clinical condition in which antibodies of immunoglobulin G (IgG) and/or immunoglobulin M (IgM) bind to red cell surface antigens and initiate red cell destruction via the complement system and the reticulo-endothelial system

(Chaudhary et al., 2014). Evan's Syndrome (ES) is the rare simultaneous or subsequent development of immune thrombocytopenia purpura (ITP) and AIHA (Dosi et al., 2012).

Lymphadenopathy refers to lymph nodes which are abnormal in size, number or consistency and is often used as a synonym for swollen or enlarged lymph nodes. Common causes of lymphadenopathy are infection, autoimmune disease, or malignancy (King et al., 2014).

B symptoms refer to systemic symptoms of fever, night sweats, and weight loss which can be associated with both Hodgkin's lymphoma and non-Hodgkin's lymphoma and also organomegaly means hepatomegaly and/or splenomegaly.

The study aims to evaluate a group of 109 patients with CLL in Western Iran (Kermanshah) on a 9-year period, and studying correlation between sex, age and overall survival in patients comparing with other countries in Asia.

### Materials and Methods

In this study, we did a retrospective analysis from 109 CLL patients that referred to Clinic of Hematology-Oncology, Kermanshah, Iran, between January 2006 and March 2014. For all of patients were calculated sex, age, survival, AIHA, Evan's syndrome, lymphadenopathy,

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organomegaly, B symptoms, white blood cell, hemoglobin and platelet by patient or pathology reports or laboratory tests.

**Statistical analysis**

Data analysis for sex and age was performed using IBM SPSS software version 19. The p-value was calculated with T- test that P<0.05 was significant. Overall survival (OS) was calculated as the time from diagnosis to death or last contact. Curve of OS was plotted by Kaplan-Meier plot in Graph Pad prism 5 Software in a five-year period (March 2009 - March 2014) with completing a two-year period and curves of OS for male and female were compared by log-rank test.

**Results**

The mean age ± SD of diagnosis for CLL patients was 60.73±10.49 years (range, 21 to 84 years) that 65 patients (59.6%) were male and 44 patients (40.4%) were female

**Table 1. The baseline characteristics in the patients at time of diagnosis of chronic lymphocytic leukemia (n=109)**

Primary variables and clinical features	n (%)	Mean± SD	P-value
Age		60.73±10.49	
			P>0.05*
Sex			
Male	65 (59.6)		
Female	44(40.4)		
Stage			
0	44(40.4)		
1	8(7.4)		
2	15(13.7)		
3	14(12.8)		
4	28(25.7)		
Autoimmune Hemolytic Anemia	16(15.1)		
Evan’s Syndrome	4(3.8)		
Lymphadenopathy	41(38.7)		
Organomegaly	36(34.0)		
B Symptoms	19(19.9)		

\* T- test

**Table 2. The Primary Clinical Variables in CLL Patients**

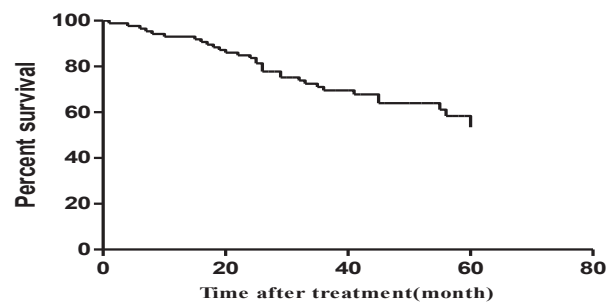
Clinical features	Mean(×10 <sup>3</sup> )	Range:[ Min to Max] (×10 <sup>3</sup> )
Platelet(count.μL-1)	160	6 to 334
Hemoglobin(mg.L-1)	123	39 to 181
White Blood Cell (count. μL-1)	53	2.5 to 300

**Table 3. Mean age and Percentage of Male for Chronic Lymphocytic Leukemia in Asian Countries**

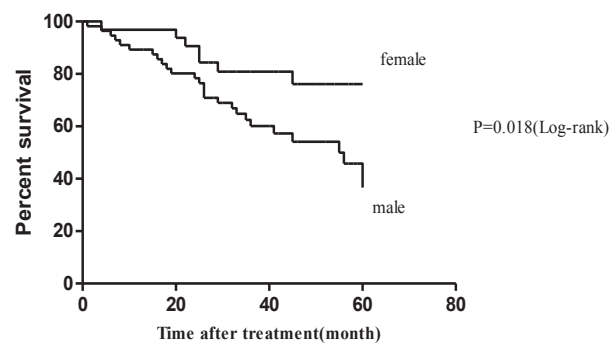
Reference	Area	Mean (year)	Male (%)
The present study	Iran( West)	60.73	59.6
Azarm et al., 2013	Iran(Center)	64	53
Kermani et al., 2007	Iran(North)	63.7	69.8
Agrawal et al.,2007	India	61	79
Durak et al., 2009	Turkey	64.3	64.5
Osmani et al., 2013	Pakistan	59.53	79
Iwatani et al., 2014	Japan	69.5	64.2
Goede et al., 2014	Russia	73	-
Pamuk et al., 2004	Turkey	63	64.5
Aozasa et al., 1991	Russia	57.5	70.3

**Table 4. Mean overall survival and survival rate (5-year period) for chronic lymphocytic leukemia in Asian countries**

Reference	Area	Mean (Month)	Survival Rate (%)
The present study	Iran( West)	38.5	64
Pamuk et al., 2004	Turkey	48	36.5
Zhu et al., 2003	China	-	81.8
Wu et al., 2009	China	48	87.3
Chim et al,2006	China	-	72
Gogia et al., 2014	India	42	51



**Figure 1. The 5-year overall survival for chronic lymphocytic leukemia for all of patients**



**Figure 2. The 5-year overall survival rate for chronic lymphocytic leukemia by sex**

(Table 1). Mean of age for female was higher than male, but there wasn't significant difference between sex and age in patients ( $P>0.05$ , 95% confidence interval (CI) -6.03 to 2.09). Based on Rai system, Forty four patients (40.4%) in our study had stage 0 and eight patients (7.4%), fifteen patients (13.7%), fourteen patients (12.8%) and twenty eight patients (25.7%) are located in stage I, stage II, stage III and stage IV, respectively. Of 109 patients, the 16 patients (15.1%) had AIHA, 4 patients (3.8%) had Evan's Syndrome, 41 patients (38.7%) had lymphadenopathy, 36 patients (34%) had organomegaly and 19 patients (17.9%) had B Symptoms (Table 1).

In our study, the mean of platelet, hemoglobin and WBC were  $160 \times 10^3/\mu\text{L}$ ,  $123 \times 10^3 \text{ mg. L-1}$  and  $53 \times 10^3/\mu\text{L}$ , respectively (Table 2). Of all patients, 22 patients (20.8%) were treated with IVIG and 46 patients (43.3%) were treated with vaccine of the Flu.

The 5-year OS (March 2009 - March 2014) for all of patients has been showed in Figure 1. Of 109 patients with CLL, 29 patients died and 23 patients were lost to follow-up before completing a two-year period and should therefore be excluded from the analysis. Survival rate for patients was 64% and mean of overall survival for 5-year period was 38.5 months.

Figure 2 shows OS rate for men comparing with women. There is a significant difference between sex and OS rate ( $P=0.018$ , 95% CI of ratio 1.14-4.65, Hazard Ratio (HR) 2.31). The survival rate for females is 78% and for males is 53.5%.

## Discussion

The CLL is the most common leukemia in adults in the Western countries. However, this disease is very rare in Asian countries (Kawamata et al, 2013; Maffei et al, 2014). CLL is caused by the accumulation of a long-lived antigen-experienced B cell clone, of which a small fraction is represented by actively proliferating cells with approximately 1-2% of cells newly generated each day (Maffei et al., 2014).

Two studies in Iran and our study (Table 3) shows that patients mean age of diagnosis is around 60 years, and also majority of patients are males. Results in Iran with other Asian countries in Table 3 are the same.

The Table 4 shows a number of studies for chronic lymphocytic leukemia in Asian countries. The 5-year mean overall survival in three countries is between 40 and 50 months and in our study is less than 40 months but the 5-year survival rate is more than 70 %, except Turkey and India.

Our study and other study (Catovsky et al., 2014) show that OS rate in females is higher than males, and in our study this comparison was statistically significant between females and males ( $P<0.05$ ). Therefore, it is probably that life conditions (smoking, hard work, etc) in males comparing with females have more affect on the appearance and mortality of CLL. In Western Iran (Kermanshah) majority of males work more than females in hard condition and smoking in males is more. In previous studies were reported that smoking (Muirhead et al., 2009) and quality of life (Shanafelt et al., 2009)

influence on development of CLL. The development of AIHA in patients with CLL is associated with specific biological features (Maura et al., 2013). Evan's syndrome and AIHA are two the main autoimmune disorders that Rossignol et al., 2010. Reported in 48 CLL patients, 26 patients (54%) had AIHA and 8 (16.7%) had Evan's syndrome. Also Mittal et al. (2008). Showed in 31 patients with CLL, 11 patients (35%) had AIHA and 2(6.4%) had Evan's Syndrome. In our study that was included 109 patients, 16(15.1%) of them had AIHA and 4(3.8%) had Evan's Syndrome. These results show that AIHA in West Iran (Kermanshah) is less than other studies and also Evan's Syndrome is different with them.

A study In India (Gogia et al., 2013) reported that Rai stage distribution in patients with CLL was: Stage 0-6, stage I-20, stage II-36, stage III-5, and stage IV-13 but in our study, more of patients had stage 0 and IV, respectively.

B-CLL is characterized by a high frequency of infections, including those of viral aetiology (Marotta et al., 1988). Infectious complications represent a major cause of morbidity and mortality in patients with CLL. The IVIG is used in a broad spectrum of autoimmune, inflammatory, and primary and secondary immunodeficiencies and the efficacy has been demonstrated in several control studies (Milani et al., 2009). Also, Influenza vaccination is recommended for patients with B-cell chronic lymphocytic leukaemia (CLL) (van der Velden et al., 2001). In our study such as other researches, immunodeficiencies and virus of the Flu were reported in patients and they were treated with IVIG and vaccine of the Flu.

First of all, CLL is a rare case of malignancy in Asian countries and lymphadenopathy and organomegaly, immunodeficiencies and the Flu virus are the main complaints in CLL. Second, in these countries, CLL is more in males and in ages of above 60 years. Third, here is not relationship between sex and age in patients. At last, OS rate in females is higher than males.

## Acknowledgements

The authors thank Mr. Gholami for technical assistance.

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