Follow Up of Sixty Patients with Chronic Lymphocytic Leukaemia

Alaadin Sahham Naji*, Bassam Francis Metti, Fouad M. AL-Kasab***

ABSTRACT:

BACKGROUND:

Chronic lymphocytic leukemia(CLL) is heterogeneous in its clinical course and typically diagnosed when patients presented with symptoms of lymphadenopathy, cytopenia ,constitutional symptoms or infection. Now 50% of patients with CLL are likely to be diagnosed when an elevated lymphocyte count is discovered incidentally **.**

OBJECTIVE:

Description of various presentation in adult patients with CLL, complications that happened during the course of their disease, cause of death and overall survival in these patients.

PATIENTS AND METHODS:

Sixty Iraqi adult patients with CLL were studied retrospectively and prospectively. These patients were assessed clinically and stratified with Rai staging, with follow up for any complications that occurred during their course of disease from time of diagnoses till last visit or death.

RESULTS:

In this study, the age group more than fifty years form 50(83.3%) patients and those less than fifty form 10(16.6%) patients. The commonest clinical feature reported was constitutional symptoms in 19(31.6%)patient. Rai staging of these patients found to be that most of patients intermediate stage II 22(36%) and advanced stage III, IV in 34(56.6%)

Regular follow up of these patients revealed that autoimmune disorder occur in 6(10%) patients, in form of autoimmune hemolytic anemia (AIHA),pure red cell aplasia (PRCA)and immune thrmbocytopenia (ITP).The increase susceptibility to infection by different viral , bacterial and parasitic infection was noticed in these patients during their course of illness. Death in these patients was due to infection with HBV and liver failure in 2(3%)patients, obstructive jaundice and hepatic encephalopathy in one(1.6%)patients, sepsis in 4(6.6%), bleeding in one (2.04%) ,renal failure in two patients (1.6%),chronic sinusitis with fungal infection and renal failure in one (1.6%)patient ,Richeters transformation and disease progression in 7(11.6%) or due to co morbid illness (stroke, ischemic heart disease, heart failure) in 3(5%) patients. The overall survival for these patients within five years was 50% .

CONCLUSION :

Constitutional symptoms was the commonest presentation of CLL Iraqi patients. The indolent course of the disease in CLL patients, still can be interrupted by different complications including infection, autoimmune disorder, and malignancy.

KEYWORD: chronic lymphocytic leukaemia.

INTRODUCTION:

Chronic lymphocytic leukemia(CLL) is characterized by the accumulation of non proliferating mature appearing lymphocyte in the blood, marrow, lymph nodes and spleen[(1)].The clinical manifestation in symptomatic patient is enlargement of lymph nodes and splenomegaly; however, hepatosplenomegaly can occur without lymphadenopathy. Anemia as presentation occurred in 15% of patients most typically normochromic normocytic and in the setting of extreme lymphocytosis[(2)] The infectious complication, increased risk of autoimmune disorders and increase risk of malignancy associated with CLL were less defined and clinically underappreciated[(3)].The initial clinical evaluation should seek to elicit a family history of lymphoid malignancy, susceptibility to infection, significant co morbid conditions, presence of bulky disease [(4)].The standard clinical procedures to estimate prognosis are the clinical staging systems developed by Rai (1975) and Binet (1981),both are based on the extent of lymphodenopathy, splenomegaly and

*Baghdad Medical College.
** Baghdad Teaching Hospital.

hepatomegaly ,presense of anemia and thrombocytopenia .These two staging systems remain the back bone of any clinical decision making for patients with CLL,they have the major advantage to be simple and inexpensive and can therefore be applied for every patient without technical equipment [5].

AIM OF THIS STUDY:

Description various presentation in adult patients with CLL, staging and complications that happened during the course of their disease, cause of death and overall survival in these patients

PATIENTS AND METHODS:

A total of sixty patients with CLL, fulfilling the criteria of CLL, were identified in the out patients clinic and in patient ward of hematology unit of Baghdad Teaching Hospital, were analyzed retrospectively and prospectively from May 1999 to July 2010. Some patients had been historically studied by previous study not published. The selection of patients done, for those who met the CLL criteria, in accordance to the recommendation of the international workshop of CLL 1989 (IW-CLL) 1.Sustained peripheral blood lymphocyte count of $>10x10^9$ \L with most of the cells being mature appearing lymphocyte. 2.Bone marrow aspirates showing greater than 30% lymphocyte[13].

Patients medical record were collected in each case regarding the mode of clinical presentation , whether he or she is asymptomatic or symptomatic in form of anemia, constitutional symptoms(Weight loss > 10% within the previous 6 months, extreme fatigue ,fevers for > 2 weeks or night sweats without evidence of infection), lymph node enlargement, infection bleeding ,abdominal discomfort, family history of lymphoprolifrative disorder or other associated disorder (psoriasis, rheumatoid arthritis) was documented.

Bone marrow aspirate and biopsy done in all patients, as part of diagnostic criteria to diagnose CLL. During the period of follow up of these patients, events and complications which happened were recorded.

Staging the patients was according to Rai system [13]

Fifteen patients had been lost contact during follow up. Survival was calculated from date of presentation till time end of the study. Statistical analyses was carried out using SPSS with Kaplan- Meier analysis to asses patients survival.

RESULTS:

Patients characteristics at time of presentation as shown in table(1).More than one half of the patients had advance disease 34(56.6%). The commonest clinical feature were constitutional symptoms in 19 (31.6%) patients followed by lymphadenopathy in frequency. Mediastinal widening recorded in 3(5.0%) patients without compression feature, two of them due to presence of lymphnods enlargement which regress back after few months of treatment and the other one due to dilated aorta.

The lab finding*: Hemoglobin*: The hemoglobin level at diagnoses ranged between 5.3-16.6 g/dl with mean level was10.3g/dl

WBC: the initial WBC ranged-from 15-672$X10^9$ / L with mean $125X10^9$.The Absolute lymphocyte count (ALC) ranged from (12.2-638) with ALC > $50X10^9$ /L in 47(78.3%)patients & ALC < $50X10^9$/ L in 23(38.3%) patients.

platelet count: on diagnoses ranged from 11-303 $X10^9$ /L with mean $159X10^9$, the platelet reduced at presentation $<100x10^9$ in18(30%) 16(26.6%) of them due to bone morrow suppression & two patients due to immune thrombocytopenia**.**

Table 1: Characteristics of CLL patients at presentation.

Patients age range <50 years >50 years	30-100 years 50(83.3%) 10(16.6%)
Median age	60 years
Male: female ratio	3.5:1
Median time of follow up	39months
Rai staging	
0	1(1.6%)
I	3(5.0%)
II	22(36%)
III	16(26%)
IV	18(30%)
Clinical presentation	
Asymptomatic	8(13.3%)
Constitutional Symptoms	19(31.6%)
Lymph node enlargement	17(28.3%)
Infection	6(10.0%)
Bleeding	2(3.00%)
Left hypochondrial discomfort	12(20.0%)
Associated diseases at presentation	
Psoriasis	1(1.6%)
Family historylymphoprolifrative disease	1(1.6%)
History of rheumatoid arthritis	1(1.6%)
Radiological and ultrasound finding	
Hilar Lymphadenopathy	3(5.0%)
Medistinal widening	3(5.0%)
Splenomegaly	50(83.3%)
Hepatomegaly	10(16.6%)
Abdominal lymphadnopathy	10(16.6%)
Ascites	1(1.6%)
Laboratory finding at presentation	
Hemoglobin(g/dl) <10 >10	 16(26%) 44(73.3%)
Absolute lymphocyte count(ALC) <50 >50	 23(38.3%) 47(78.3%)
Platelet *(x10^9/L)* <100 >100	 18(30%) 42(70%)

Complication related to hemopoietic elements including autoimmune hemolytic anemia(AIHA) with direct coombs test (DAT) positivity recorded in 3(5%) patients, one of them at initial presentation and others during course of illness accompanied with autoimmune thrombocytopenia Table(2).

Table 2: Autoimmun abnormalities complicated the course of illness.

Autoimmune disorder	NO.	%
Auto immune hemolytic anemia	3	5%
Immune thrmbocytopenia	2	3%
Pure cell aplasia	1	1.6%

Other disease related complications**:** Patients with CLL have an increased risk of numerous disease related complications; these include infection, thrombosis, disease progression including Richter's transformation, malignancy(in two patient recorded with brain and bladder tumor),. Table (3and4). Pleural effusion was recorded in 4(6.6%) patients, one of them due to disease itself, documented by cytology, and others either due to parapneumonic, heart failure and in one patient due to renal impairment.
Ascitis was found in one patient at initial presentation associated with pleural effusion due to renal impairment, while 4(6.6%) patients had ascitis during their course of illness, 3(5%)of them because of chronic hepatitis B(HB-virus)virus infection and one of them due to huge splenomegaly and portal hypertension with reversal flow.

Table 3: Types of infections that happened during follow up.

Type of infection	NO.	%
Herpes zoster	3	5.0%
HBS Ag +	4	6.6%
HCV-antibody +	1	1.6%
Recurrent chest infection Pneumonia Tuberculosis	 4 3	 6.6% 5.0%
Recurrent G.I infection	4	6,6%
Recurrent Skin infection	3	5.0%
Hydited cyst of the liver	1	1.6%
Chronic fungal infection of paranasal sinuses	1	1.6%

Table 4: Other complications that documented during follow up.

Other complications	NO.	%
Ascites	4	6.6%
Plural effusion	4	6.6%
Pulmonary embolism	1	1.6%
Testicular swelling	1	1.6%
Need frequent transfusion	3	5.0%
Progression to CLL/Prolymphocytic	1	1.6%
Progressive disease	6	10%
Skin infiltrate	1	1.6%
Associated malignancies	2	3.0%

Death occurred in 22(36.6%) patients after median follow up time of (39) months, The cause of death in these patients is either liver failure due recent infection or reactivation caused by immunosuppression due to disease itself or chemotherapy,disease progression or sepsis. Other cause of death which are unrelated to CLL but due to concomitant co morbid illness like stroke and ischemic heart disease,Table (4)

Table 5: Cause of death .

CAUSE	NO.(22)	%
Bleeding	1	1.6%
Sepsis	4	6.6%
Liver failure Chronic hepatitis B Chronic hepatitis C Obstructive cause	 3 1 1	 5.0% 1.6% 1.6%
Disease progression	6	10.0%
Richeters transformation	1	1.6%
Renal failure	2	3.0%
Ischemic heart disease	1	1.6%
Heart failure	1	1.6%
Stroke	1	1.6%

The median survival of these patients was 69months with the 5 years survival of these patients was 50%as shown in Figure (1) .

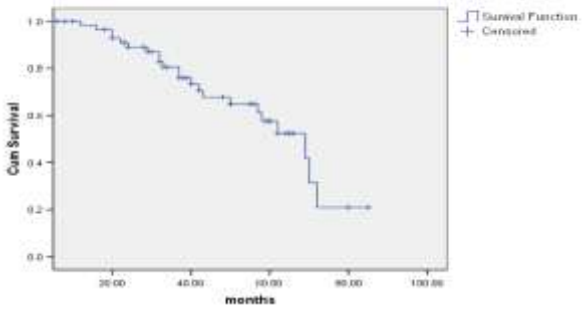

Figure 1: Overall survival of 60 patients with CLL with variable Rai staging.

DISCUSSION:

CLL is the most common leukemias in the western world and is twice as common as CML and this disease accounts for nearly 30 percent of all leukemias at any point in time[6].

The reported median age in this study was comparable with mean age in reports from USA, Italy, Germany with age ranging from 61-65 year [7] and patients age more than 50 year in 86% with other Iraqi studies[8].

Constitutional symptoms were recorded as a commonest clinical feature with high percentage of this presentation in our population which may explained in that the majority of Iraqi patients had progressive or advance disease at the time of diagnosis and this is what had been registered by other Iraqi study of CLL patients in 1997[8].In contrary what's known in that fever and weight loss are uncommon feature in CLL in comparison with non Hodgkin's lymphoma,in which constitutional symptoms occur in 25% of patients[1,4].

Lymphadenopathy as presenting feature occur frequently in CLL patients which may be localized or generalized. In this study it was documented in more than one region in19(31.6%), while in 10(16.6%) patients only it was localized to one region and lymphadenopathy asfrequent presentation found in other Iraqi studies [8,9]. Abdominal lymphadenopathy had been registered in this study concomitantly with peripheral lymphadenopathy as it is rarely to find large Para

aortic nodes in patients with CLL without peripheral lymphadenopathy [10]. Mediastinal widening was recorded with lympadenopathy without compression feature as it is known that involvement of mediastinal lymph nodes in CLL, un likely in lymphoma, rarely results in superior vena cava syndrome. There are several reported cases of CLL patients in whom the enlargement of the mediastinal lymph node is a manifestation of the so called Richter's transformation [11] which had not been documented in this study.

In this study anemia was mainly due to heavy bone marrow infiltration rather than other cause of anemia like an autoimmune disorder as a causeof anemia. Even so other causes of anemia should be excluded in these patients, like hypersplenism, and in elderly folate and B12 deficiency and this may be prognostica lly important as in some studies, they found that anemia is one of important prognostic feature beyond bone marrow pattern and hepatomegaly [12].

The increase incidences of infection in patients with CLL by various type of infection(bacterial,viral,parasitic) were reported and whether this attributed to the disease itself or as consequences of treatment either as initial presentation in form of chest infection or skin infection (herpes zoster infection) or they may have recurrent infection during course of their illness. As the infective complication are a common clinical problem in CLL ,with an incidence of 0.26-0.47 per patient year ,accounting for up to 50% of all CLL related death and this increase susceptibility to infection are both resulting from hypogammaglobulinaemia ,nuetropenia ,impaired T and natural killer cell function and defective complement activity[4].

In this study, four patients after many courses of chemotherapy presented with ascitis and positive HBS Ag , actually these patients did not have baseline virology screen and did not have marker for HBV reactivation like HBV DNA, or liver biopsy. We do not know whether these patients had originally infected with reactivation or they are acquired from blood transfusion that they received during their course of disease. Cancer chemotherapy – induced reactivation of hepatitis B virus (HBV) replication with subsequent hepatocellular damage is a well known complication [14].So that prophylactic therapy with nucleoside analogues for those HBSAg positive patients seems logical to prevent irreversible hepatic damage during cytotoxic or immunosuppressive therapy [15].

Extranodal involvement by leukemic cells may be symptomatic when it develops in certain location. Leukemic cell infiltration of lung parenchyma producing nodular or military pulmonary infiltrate that can be detected by X-ray film, leukemic infiltrate of the pleura may result in hemorrhagic or chylus plural effusion[2].

Extra nodal involvement was recorded in form of skin infiltrate , pleural effusion which proved cytologically which showed infiltration by mature looking, small malignant lymphocyte, responding to treatment with alkylating agent.Testicular involvement presented as testicular swelling with raised possibility of infiltration by Ultrasound not confirmed by biopsy responding to treatment with purine analogue.Renal infiltration with renal impairment with addressing of renal involvement by increase ecchogensity by ultrasound .Leukemic cell infiltration of renal parenchyma can be detected in more than half of all patients examined postmortem, however, CLL only rarely is associated with impaired renal function [2].

Autoimmune disorders had been reported and this raise the point that CLL is not only a malignant disease but also a complex immunologic disease. The paradoxical finding of immune deficiency and autoimmune phenomena have been hallmarks of CLL [16].

Rai staging in this group of patients showed advanced stage(III,IV) in the majority of the patients in more than half of them ,and these patients had been treated by various types of therapy including alkylating agents and some of them with purine analogue containing regimen with overall survival in these patients it looks higher as what is known with median survival was 69 months and 5years survival about 50%. As it is known survival in CLL patients can ranged from long term median survival in low risk patients up to 25 years to few years in those with poor prognostic criteria including the advanced stage with 5 years survival rates in advance stage just only 14 %, and median survival ranged from 1-3 years [7].

CONCLUSION :

CLL Iraqi patients usually present with advance stage and despite the indolent course ,disease still complicated by many infections, and autoimmune diseases.

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