Original Article

Outcome of 49 Iraqi adult patients with Chronic Lymphocytic Leukemia treated with oral alkylating agent:

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Summary:

Background: Chronic lymphocytic leukemia (CLL) is a heterogeneous disease with an extremely variable course. Survival after diagnosis can range from months to decades and wide variability exists in the rate of disease progression and the incidence of disease-related complications among patients with CLL. Staging helps to define prognosis and to decide when to initiate therapy.

Objective: To asses response to oral alkylating therapy and to evaluate the adverse events that can complicate the disease itself or the treatment, including infections, autoimmune and other complications. The survival events are also been assessed.

Patients and methods: Forty nine Iraqi CLL patients, their age ranged between 40-90 years were followed with median duration of 28 months. During the follow up period of these patients, the events that complicated the disease or therapy were recorded. The primary endpoints were response rates, quality of response, Secondary endpoints of the study were overall survival , progression-free survival and event free survival. Response rates were calculated for 40 patients who were treated for at least 6 months. All patients were treated with intermittent pulse therapy of oral single alkylating agent.

Results: The majority of patients recruited either had intermediate or advanced stage disease in 45(91%) patients .Autoimmune phenomena, were documented in 5(10.2%)patients. There was increased incidence of infections with either viral or bacterial pathogen, complicating the course of disease in 20 (40.8%). Remission state was mainly with partial response in 26/40(65%).In12(24.4%) patients the disease progressed and death occurred in 6(12.2%) patients ,4(8.1%)of them were CLL(related) and 2(4.08%)of them unrelated(stroke, ischemic heart disease) to CLL with median progression free survival(PFS)and overall survival(OS) for these patients were not reached, with 2 years PFS and OS were70%.

Conclusion: Although CLL is an indolent disease still the course is complicated by many events like autoimmune problem and infections whether related to CLL or to treatments. Alkylating agent were effective therapy in the treatment of CLL and the majority of patients in this study partially responded

Key word: Chronic Lymphocytic Leukemia : Alkylating agent.

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Introduction:

Chronic lymphocytic leukemia was reported to be the most common leukemia among older adults in Western countries, accounting for approximately 30% of all leukemias and approximately 10% of hematological neoplasms.(1). In the 1950s only 10% of CLL cases were identified from a routine blood count (2). When the Rai staging criteria were introduced in the mid 1970s, individuals with stage 0 disease were required to have a lymphocyte count about 15,000 per mm3. Twenty years later CLL criteria required a lymphocyte count above 10,000 and the National Cancer Institute (NCI) criteria above 5000 lymphocytes per mm(3). Two major staging systems have been developed, each having established value in helping to predict survival (4). Rai and colleagues introduced the first widely used staging system in 1975. This staging system designated five clinical stages using 0 and Roman numerals I through IV .Intermediate- and high-risk patients have median survivals of approximately 90 months and 19 months, respectively (5).Patients with CLL are prone to develop systemic autoimmune disease. The most common autoimmune disorders result from autoantibodies that are directed against hematopoietic cell antigens, such as those found on red blood cells or platelets, although other types of autoimmune disorder also appear more common among CLL patients than in the general population (6,7).Monotherapy with alkylating agents has served as initial, front-line therapy for CLL for several decades, which likely produces its antitumor effect by binding covalently with DNA, RNA, and cellular proteins (8). Chlorambucil has been considered the "gold standard" for several decades.Even today, this drug remains an appropriate option, particularly in unfit, elderly patients. The advantages of chlorambucil are its low toxicity, low cost and convenience as an oral drug; its major disadvantages are its low to non-existent complete remission and some side effects that may occur after extended use (prolonged cytopenia, myelodysplasia and secondary acute leukemia(9).

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Patients and methods:

A total of forty nine patients with CLL, fulfilling the criteria of CLL, were identified in the outpatients clinic and the inpatient ward of hematology unit in Baghdad Teaching Hospital, patients were analyzed retrospectively and prospectively. The

study was initiated in July 1999, and recruitment was stopped in September 2006 with median duration of follow up was 28 months. The selection of patients for those who met the CLL criteria was in accordance to the recommendation of the international workshop of CLL 1989 (IW-CLL) (Sustained peripheral blood lymphocyte count of >$10x10^9$ \L with most of the cells being mature appearing lymphocyte,Bone marrow aspirates showing greater than 30% lymphocyte). The stage of the disease was assessed according to the Rai classifications, stage 0 lymphocytes only, stage I lymphadenopathy, stage II splenomegaly and/or hepatomegaly with or without lymph node enlargement, stage III anemia below 10g/dl, irrespective of physical sign, stage IV thrombocytopenia below$100x10^9$/L with or without any of the above feature. During follow up period of these patients, the events and complications that complicated the disease or therapy were recorded. The primary endpoints were response rates, quality of response, Secondary endpoints of the study were overall survival ,progression-free survival and event free survival . Response was assessed in40 patients ,those who had received therapy for at least six months..All patients were treated by intermittent pulse therapy with oral single alkylating agent(either chlorambucil or cyclophosphamide) with steroid for 5-7 days and cycles were repeated every 21-28days in the era that Fludrabine was not available and difficult to access by patients . After six months of therapy, patients were evaluated by clinical examination and blood count , serum chemistry , bone marrow biopsy or aspirate was recommended for confirmation of complete response but it was not due to patients refusal .During follow-up response was stratified as complete response (CR),partial response (PR) and no response(NR).Response with (CR) was defined as absence of lympadenopathy ,a lymphocyte count of less than 4000 per cubic millimeter ,hemoglobin concentration of more than 100g per liter, platelet count of more than 100,000 per cubic millimeter. A partial response (PR) was defined as a reduction of at least 75% in the initial lymphocyte count and at least 50% of the initially enlarged lymph nodes. No response or failure to treatment(NR) was defined as lack of a reduction of at least 50% in the enlarged lymphnods ,or the lack of a reduction of at least 75%in the absolute lymphocyte count. Overall survival was calculated from randomization to death, progression-free survival from randomization to the time of disease progression or death ,while event free survival, any events had happened during the patients course, either recurrent infection ,repeated needs of blood components, pulmonary embolism, and malignancy. Time to event was estimated using the Kaplan-Meier method.

Results:

total of 49 Iraqi patients with CLL were enrolled in this study .Age ranged from 40-90 years, with median age was 62years. The male to female ratio was 3.5:1, with median time of follow up (28) months. Rai staging of these patients found that most of patients were with stage II 19(38.70%), and stage III, IV formed 26(53.06%).

Table (1): demonstrate characteristics of forty nine patients with CLL

Variables	
Age ranged	40-90 years
Median age	62 years
Male:female ratio	3.5:1
Median duration of the follow up	28 months
Rai stage II	19(38.7)% patients
Rai stage III,IV	26(53.0)% patients

Response to treatment was evaluated in 40 of the 49 patients of the treated group who were alive and treated at six months with overall response in 77.5%, partially responded in 65%,and complete response in 12.5%.Table(2). Those patients failed response to treatment in 22.5%,2(4.0%),4(8.1%),1(2.0%) of them treated with COP,CHOP and FC respectively .

Table (2): type of the response in CLL patients treated with oral alkylating agent assessed in forty patients after six months of treatment

Response	NO./ (40 patients)	%
Complete response	5/40	12.5
Partial disease	26/40	65.0
No response	9/40	22.5

The events that complicated the disease and therapy with oral alkylating agents had been registered concerning autoimmune, infections and other complications that diagnosed at presentation and occurred during and after treatment as shown in table (3), (4),(5) .

Table (3): Autoimmune manifestations complicated the disease and pre and post initiation treatment in patients with CLL

Autoimmun disorder	NO.	%
AIHA	2/49	4.08%
ITP	2/49	4.08%
PRCA	1/49	2.04%

Table (4): types of infections that registered during follow up of these patients complicated their course whether related to treatment or disease itself

Type of infection	NO.	%
Herpes zoster	3/49	6.1%
HBS Ag +	4/49	8.1%
Recurrent chest infection	6/49	12.2%
Recurrent G.I infection	4/49	8.1%
Recurrent Skin infection	3/49	6.1%

Table (5): Other complications that documented during follow up.

Pulmonary embolism	**1/49**	**2.04%**
Testicular infiltrate	**1/49**	**2.04%**
Need frequent transfusion	**3/49**	**6.1%**
Skin infiltrate	**1/49**	**2.04%**
Other malignancies	**1/49**	**2.04%**

Progression of the disease occurred in12/49(24.4%)patients, with re enlargement of lymphnodes or hepatosplenic enlargement and lymphocytosis, and six patient were died.The median PFS was not reached and 2 years PFS 70% Figure (I) and those who had progression were obliged to change their treatment to COP,CHOP in the era where fludarabine was still not widely available for use.

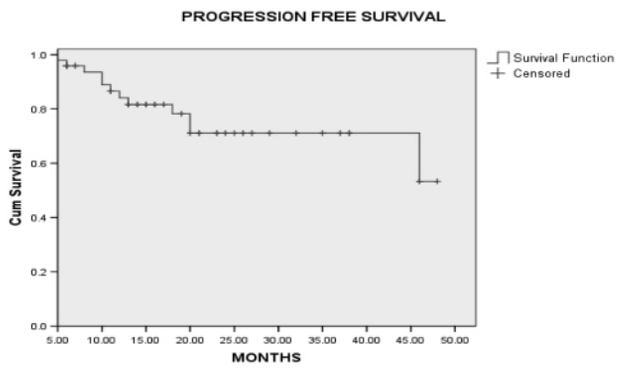

Figure (2) Progression free survival in 49 patients with median follow up duration 28 months

Many events that complicated the course of these patients, either related to CLL itself or as a complication of the therapy . In 32 (65.5%) patients, they had recurrent infections, repeated needs of blood or platelet transfusion, pulmonary embolism autoimmune disease and other malignancies. with median event free survival was (months± SD) 14±1.169 months, and 2 year EFS was 25%.Figure (2).

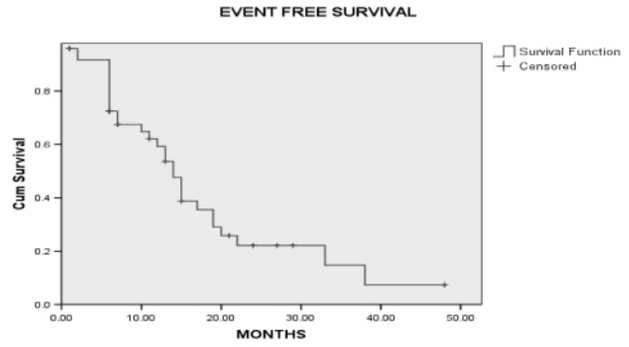

Figure (2): event free survival for CLL patients.

The cause of death which was either related to CLL or unrelated. Death occured in 6(12.24%)patients after median time of follow up with 28 months, The cause of death in these patients was either infection with hepatitis B virus infection complicated by liver failure in 2(4.08%), bleeding in 1(2.04%),and 1(2.04%) with sepsis. In two patients the cause was unrelated and it was due to co morbid illness with stroke and ischemic heart disease. The median overall survival for these patients not reached with 2years survival about 70%.. Figure (3).

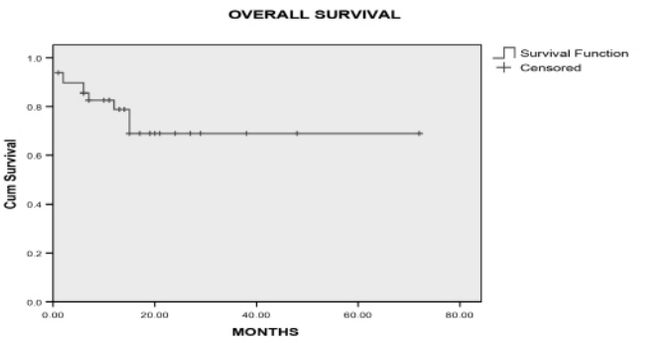

Figure (3) overall survival in 49 patients with CLL treated with single alkylating agent.

Discussion:

Patients with CLL are prone for developing many complications during their course whether it is related to treatment or disease nature itself. The increase incidences of infection in patients with CLL by bacterial and viral infection were reported .In20 (40.8%) patients they had infections during their course of their illness, either recurrent chest infection, skin or gastrointestinal. These infections caused either by viral infection(like hepatitis B virus infection, herpes zoster),bacterial, mycobacterium infection. Infective complication were 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. The increase susceptibility to infection is both intrinsic to the disease and therapy related, resulting from multiple factors including hypogammaglobulinaemia ,nuetropenia,impaired T and natural killer cell function and defective complement activity(10) After many courses of chemotherapy ,4 (8.1%) patients presented with ascitis and enlarging spleen and were found to be HBS Ag positive, actually these patients did not have baseline virology screen and did not have markers for HBV reactivation like HBV DNA, or liver biopsy. We do not know whether these patients were originally infected and they had reactivation or it was acquired from blood transfusion that they received it during their course of illness. Cancer chemotherapy – induced reactivation of hepatitis B virus (HBV) replication with subsequent hepatocellular damage is a well known complication(11).with response to INF-α treatment in high (HBV DNA) level is poor (12). five(12.5%) patients evolved Tuberculosis(T.B)after treatment with alkalyting agents,however no death was registered due to T.B.despite it is mentioned that Fungal, mycobacterium, and cryptococcal infections are uncommon in those treated

with alkylating agent and its noted more common in patients treated with purine analogues, such as fludarabine, who apparently have an increased incidence of infection with other opportunistic organisms(13) Extranodal involvement by leukemic cells infiltrate may be symptomatic when it develops in certain locations, such in the retro-orbit, prostate, pharynx, and lung parenchyma or pleura which may result in hemorrhagic or chylus plural effusion or asymptomatic with leukemic cell is frequently detected at autopsy(14). Extra nodal involvement was recorded in the form of skin infiltrate in one patient, massive pleural effusion in one patient documented cytologically which showed infiltration by mature looking, small malignant lymphocyte, one patient had testicular swelling (not biopsied but by suggestion of ultrasound),two patients during their disease progression had renal impairment with increase echogenisty by ultrasound suggesting renal infiltration by the disease. Autoimmune hemolytic anemia(AIHA) was reported in two patients with direct coombs test (DAT) positive one of them on initial presentation and other during the course of illness. The other two patients develop autoimmune thrombocytopenia, again one of them was diagnosed on initial presentation and the other had I.T.P with coombs test positive while he is on treatment. Pure red cell aplasia (PRCA) developed in one patient while the patient was on treatment, with frequent blood transfusion. 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(15). The potential role of T-cell defects in inducing autoimmune complication in B– cell CLL has been stressed by increased frequency of AIHA in patients treated with Purine nucleoside analogues like fludarabine. These drugs induce severe depletion of the CD4 cell subset and to lesser extent the CD8 subset(16). Warm AIHA, ITP, pure red cell aphasia (PRCA), occur with incidence of 4- 40 %, 1-2 % and < 1% respectively (10). Nine 9(22.5%) patients had no response to treatment . The response to treatment may be affected by many factors including alteration in genes such as p53,mdm-2 and bax which control entry into apoptosis which may cause drug resistance(17). The response in this study was documented in 77% which was mainly partial response. Other studies showed that the overall response rate with these drugs is 40 to 60%, with 4 to 10% of patients achieving a CR (18,19). again Polish Group, combination of chlorambucil with steroid showed CR in 12%,PR45%(20).in this study Cyclophosphamide has also been used in the treatment of CLLpatients which differs little, if at all, from chlorambucil in its effectiveness (21). Progression occured in 12/49(24.4%) with 2 years PFS was 70%, all of these patients were in advanced stage(Rai stage III,IV) and universally they partially responded patients, so this may support the idea that getting more complete remission with new treatment like fludarabine we may get better PFS. Despite 91% of patients enrolled in this study had intermediate and advanced Rai staging system treated by intermittent pulse therapy (less myelosuppression) ,the 2 years survival for these patients was about 70% (Six patients had been dead ,four of them were CLL related, and the other two from unrelated cause). In two. Other studies revealed that the 5 years survival rates in those with advance stage was only 14 %, with mean survival 3.3 years(22). This difference in the survival from what mentioned in other studies, may be due to median duration of follow up was shorter than other studies, small randomized numbers of patients other parameter like tumor burden, disease aggressiveness, age and different disease biology, or use of pulse therapy(less myelosuppressive) rather than daily administration, despite it was mentioned that the response rate to chlorambucil is highly dependent on the dose of drug used (23).

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