RESEARCH COMMUNICATION

Chronic Lymphocytic Leukemia in the Recent 10 Years and Treatment Effects of Fludarabin

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Abstract

Objective: CLL (Chronic Lymphocytic Leukemia) is the most common form of leukemia in the western world and because of prolonged survival of patients, the prevalence is high. Chemotherapy is usually not indicated in early and stable disease and using Chlorambucil with or without steroids has been the drug of choice in the treatment of CLL for many years .Clinical studies have shown that using Fludarabin can cause a complete response in significant number of untreated and/or previously treated CLL patients. The aim of this study is evaluating of CLL patients and determining the effects of treatment with Fludarabin. Methods: A retrospective (descriptive/cross sectional) study of CLL patients who admitted to Hematology and Oncology Research Center of Tabriz university of Medical Sciences, between 1995-2005 was made and 126 patients enrolled. Collection of data was carried out according to special questionnaire and response to Fludarabin was analyzed by SPSS 11 software. Results: The patients mean age of diagnosis was 63.7 years (SD=8.9), 69.8% were males. Illness and fatigue were the commonest presenting symptoms in 54% and lymphadenopathy was the most common clinical sign in 88.9%.Most of the patients were in stage C in Binet system (52.4%) and/or stage IV in Rai system (44.4%).Chemotherapy with chlorambucil and Prednisolone was the most common regimen used (60.3%) and 49.2% of patients were in partial remission with this treatment. Forty two patients treated with Fludarabin and 50% were in partial remission, 35% in static disease, 10% in progressive disease and 5% in complete remission (P=0.053). Conclusion: The median survival with Fludarabin was 43.9 months (SD=27.2) and in the case of Chlorambucil+Prednisolone and CVP or Chop it was 45 months (SD=26.5) and 50 months (SD=32.2), respectively (P>0.05). P value in the relationship with survival and response to Fludarabin was more than 0.05.Above all, Fludarabin is the choice treatment as first and second line therapy, as well as for patients who have failed therapy with standard regimens.

Key Words: CLL - Fludarabin - remission

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults worldwide (Johnston, 1998).

It affects one in a 10,000 in the United States of America annually(Saven and Piro, 1994).

The accumulation of mature appearing and non proliferating CD5+ B lymphocytes in blood, marrow, lymph nodes and spleen are seen in this disease (Johnston, 1998) CLL is the disease of older age group with pick incidence between 50-55 years of age.

It affects males twice than females (Park and Koeffler, 2001;Kasper et al., 2005). The etiology is unknown but genetical factors may play a role (Johnston, 1998). Because all treatmental approach are some sort of harmful so selecting the patient who is essentially in need of treatment is quite mandatory before starting any medication. Even though the treatment of Rai stage 0 or Binet stage A disease can hinder progression but increases the rate of epithelial tumors (Johnston, 1998).

In a study on CLL cases in stage 0, treatment with or without Chlorambucil plus Prednisolone , had no long term survival benefit. The results of this study emphasized that the CLL patients who are in early phase of their disease can be observed without any medication till the progression time (Park and Koeffler, 2001; Robak and Kasznicki, 2002).

As a whole patients in progression with low or moderate risk and high risk disease will have longer survival if they respond to therapy (Johnston, 1998). Early stage or stable disease need not any treatment and should be observed every 3-4 months but advanced or symptomatic cases need medical intervention. Nowadays, in spite of introduction of new agents using chlorambucil as an alkalizing agent is still routine and combination chemotherapy is also tried in refractory cases.

Fludarabin is a purine analog and plays an increasing

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role in treatment of CLL in first line (Keating et al., 1998) and or in second line for treating refractory CLL or even who have relapsed after therapy with Fludarabin, because 75% of such cases again respond using it. Fludarabin also is used in CLL patients who are candidates for stem cell transplantation .This drug is highly active in CLL cases and using (25-30mg/m2 IV daily for five days)results in 45-48% total and 13-38% complete response after 6 cycles of therapy.

The main toxicity of Fludarabin is bone marrow suppression and infection in patients who have received alkalizing agents beforehand but nausea, vomiting and neuropathy is rare .Because of the high percentage of immune hemolytic anemia, thrombocytopenia and aplasia, it is wise to check CBC regularly. For reducing its toxicity, Fludarabin is given 30mg/m2 per day IV for 3 days and repeated every 4 weeks that in comparison with standard five day regimen shows lower total response (40%) and only 10% complete response but has been resulted in significant decrease in infection rate. Regarding survival there is no significant difference between two regimens. Nevertheless, therapy with Fludarabin can cause complete remission in significant number of non treated CLL cases or in previously treated one (Keating et al., 1998). In spite of conservative concept of treatment in early stage disease , treatment with using BRM (Biological Response Modifiers)and stem cell transplantation thereafter specially in younger patients has implanted hopes in control and treatment of these patients. In this study we reviewed the files of all CLL patients in Tabriz Hematology and Oncology Research Center in last ten years and studied them regarding demographic and treatment strategies and evaluated the response rate of Fludarabin treatment.

Materials and Methods

For evaluation of response to treatment and survival of patients with CLL in Hematology and Oncology Research Center of Tabriz University of Medical Sciences in last ten years and the relation of some varieties such as age, sex, stage of the disease, blood groups and so on this study planned to run. The files of all cases of CLL patients (126) who had referred as an out-patient or in-patient, reviewed. In this descriptive – cross sectional study, data were extracted using a questionnaire consisting information about demographic characteristics of the patients, such as (age, sex, job, date of diagnosis and etc), physical signs at presentation like(fever, dyspnea ,cough ,weight loss, abdominal pain, anemia, hepatosplenomegaly, lymphadenopathy and etc. Laboratory data including (WBC, Neutrophil and lymphocyte count, Hb, Hct, Plt LFT, KFT, Blood grouping) and chest X Ray, abdominal sonography at presentation , stage and regimen, number of chemotherapy cycles or untreated control cases and survival rate. Then response rate to Fludarabin regarding CR, PR, ST, PD was calculated. The extracted data coded and analyzed using SPSS software, chi-square ,one way Anora and T-Test. In evaluation of the variables, $p < 0.05$ recognized to be significant.

Results

The files of one hundred twenty six CLL patients were reviewed. 88 of them (69.8 %) were males. The mean age of the all patients was 63.7 ± 8.9 year. The age range of this disease varies from 41 to 80. OF the 70 patients with Blood group checked, O+ and A+ with 37.1% and 34.3% were the dominant blood groups respectively which had the same pattern of distribution as the community was. From the point of symptoms at presentation fatigue with 54% was the commonest and dyspnea(31.7%), abdominal pain(28.6%), weight loss(22.2%), perspiration(19%), itching(14.3%), palpitation(14.3%), dizziness(11.1%), bleeding(6.3%), nausea and vomiting(4.8%), skin rashes(4.8%) and adenoids enlargement (16%) followed it .

Among the signs at presentation, lymphadenopathy found in 88.9% of the patients that in 55.4% of them involvement of all three axillary, cervical and inguinal nodes noted. Involvements of cervical and axillary were the second commonest site. As an isolated lymphadenopathy cervical nodes with (8.9%), axillary with (3.6%) and inguinal nodes consist (3.6%) of the cases. In 11.1%, there was no lymphadenopathy at presentation. Splenomegaly (67.2%), anemia (63.5%), thrombocytopenia (47.6%) and hepatomegaly with 32.8% were the most common signs at presentation. The mean WBC at presentation was 117492.5/ml and for lymphocytes and neutrophils, differentiation count was 76.15% and 11.18% respectively. The minimum count of platelets at presentation was 4000/ml and maximum was 434000/ml (mean 128682.54). Minimum and maximum range of the hemoglobin and hematocrit and mean Hb/Hct were 3.5 gr/dl, 13.5% and 17 gr/dl, 51%, 10.37± gr/dl and 33.82± 8.4% respectively. Most cases were in stage C of Binet classification (stage A=22.2%,stage B=25.4%,C=52.4%) and regarding Rai staging system most of the cases were classified as having stage IV at presentation (stage 0=1.6%, I=11.1%, II=23.80%, III=19% and stage IV=44.40%). As a whole 5 forms of drug or combination used in the first line of treatment, but the combination of Chlorambucil and Prednisolone was the commonest with 60.30%.

Others were CVP/CHOP (23.8%), Fludara (7.9), Cyclophosphamide (3.2%), 2CDA (3.2%).Only 1.6%of cases were on watch and wait program. Forty two patients received Fludarabin as first or second line therapy which accounted 36.2% of CLL cases .From the point of response to therapy most of the patients (62 cases,49.2%)were in partial response (PR),36cases (20.6%) in static stage ,16(12.7%)in complete response (CR)and 14(11.1%)were in (PD)progress disease stage .We could not estimate the response of the 8 patients (6.3%) from their files .In follow up of the patients for evaluating their survival ,44 patients found to be dead of their disease , 40 were alive and in spite of frequent calling for about 42 of them we could not get in touch and so could not get any notion of their living status. Of 34 CLL patients received Fludarabin, 18(52.9%) died and 16 cases (47.1%) were alive at the time of study ($p>0.05$).

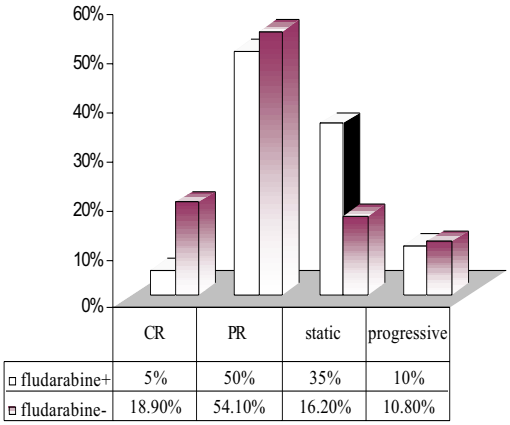

Figure 1. Evaluation of Response to Treatment of CLL Patients in two groups based on the type of treatment they received

We divided the patients into two groups based on the type of treatment they received .Those who got Fludarabin alone and the patients treated with various kinds of antineoplastic agents (Chlorambucil+ Prednisolone ,CVP,CHOP,Cyclophosphamide,2CDA),or just controlled without any medication.Statistical analysis showed no difference in terms of response rate between two groups that most of them were in partial remission state (P=0.03)(Fig 1).

The highest survival depends on the type of treatment seen in those who received CVP or CHOP chemotherapy.The mean survival of these patients was 50.3±32.2 (6-107) months.This figure was 19.5±6.5(12-26) months.The mean survival of CLL patients treated with Chlorambucil+Prednisolone was 45±26.5(4-98) months and those with 2CDA and Cyclophosphamide was 42±13.8(30-54) and 48.5±27.1(25-72) months respectively(P>0.05).

Regarding response to treatment and shape of the disease it was shown that the most cases with Rai Stage I and II were in PR ,and needed PD in lower stages. Most of the higher stages (III , IV) were in SD and PD (P=0.20).In evaluation of response to Fludarabin and stage of the disease in Binet staging system most of the cases in stage A had CR or PR which consisted 20 and 60% respectively.In this stage there were not any cases in PD.Stage B cases were in PR in 42.9% and the rest of cases were in static and PD state .Stage C cases were in PR and SD state with 50 and 35% , 10% of cases in PD and 5% in CR(P=0.06).Hepatomegaly had significant statistical relation with response to Fludarabin (P=0.03).Between response to Fludarabin and existence of other symptoms and signs there was no statistical relation (P>0.05).These results were extracted regarding lab data and response to treatment (Table1).

Table1. Relation between Laboratory Data and Response to Treatment in CLL Patients

Lab	Response	Mean ± SD	P value
WBC	CR1	50637±52183	0.045
	PR2	125581±123219	
	SD3	89683±87560	
	PD4	165505±206085	
Lymphocyte	CR	74±19	0.697
	PR	77±11	
	SD	73±20	
	PD	76±15	
Neutrophil	CR	23±20	0.001
	PR	7.8±6.7	
	SD	13±17	
	PD	9.9±10.4	
Hematocrit	CR	41.9±4.7	0.000
	PR	31.4±8.1	
	SD	36.9±5.8	
	PD	28.5±9.5	
Hemoglobin	CR	13.6±1.6	0.000
	PR	9.7±2.8	
	SD	11.5±2.1	
	PD	8.8±3	
Platelet	CR	158875±57281	0.026
	PR	118483±82321	
	SD	161692±96605	
	PD	98142±53012	

1- CR: complete remission 2- PR: partial remission 3- SD: static disease 4- PD: progressive disease

Discussion

Chronic lymphocytic leukemia is the disease of older age group with pick incidence of 50-55 year, that affects males twice than females (Johnson, 1998). In this study we evaluated 126 CLL cases who referred to oncology center of Tabriz in the last 10 years. Most of the cases were men with the mean age of 63 years.

Nowadays, because of routine check ups and performing blood tests, the number of non symptomatic cases diagnosed with CLL are raising up to 40% but based on references fatigue ,enlarged lymph nodes and recent infections are still the common causes of seeking medical consultation (Johnson,1998).In our study the most common complaints were, fatigue, dyspnea and abdominal pain.

There is no clear relation between age and sex with response to treatment in CLL patients .A study by Molica and colleagues showed that 53 patient with the age of less than 50 had better survival than 201 cases with the age of more than 50 years old and females survived longer than males.

Some other studies showed that women have better prognosis than men regardless of age and stage of the disease (Johnson, 1998). There was not any significant difference between age and response to treatment in all 4 stages in our study and in spite of the fact that most of the men had CR or PR, but had better response than women that mostly were in SD or PR . Leporrier study in 2004 showed equal efficacy of Fludarabin in CLL patient younger than 65 years and older regarding response to treatment (Leporrier, 2004).

In randomized studies, comparison between COP regimen and Chlorambucil showed there isn't any difference in survival and CR. In another study survival and CR for two groups (COP and Chlorambucil +Prednisolone) were similar (Johnson, 1998). In our study

the highest survival obtained with COP or CHOP and there was not any significant statistical difference between survival and the kind of regimen used in all groups .The mean survival with CVP or CHOP and chloambucil + prednisolon was 50 and 45 months respectively.

Till 1990 less than 5% of CLL patients could reach CR but during last 15 years significant changes have occurred in their treatment in a way that with modern treatments about 50% of the patients achieve CR.

This success is mostly due to new drugs used in control of these patients such as [Fuldarabin,Pentostatin ,Cladribin and Monoclonal antibodies Rituxinab,Alemtuzmab].Even combinations of these drugs result in better response than using as single agent (Lamanna, 2005).Now, monotherapy with Fuldarabin is an accepted therapy for CLL patients comparing with other drugs such as alkalizing agents or corticosteroids. In our study 42 patients received Fludarabin as first or second line. Most of the cases got PR .Survival of the patients treated with Fludarabin was 43.9± 27.21 months that did not show statistical significant difference.

The reason may be related to the paucity of cases or poor data collection.

In a study done in Italy by Stelitano and colleagues in 1999,47 patient with CLL treated with mean 6 course of Fludarabin (2-12 coures) and in a 13- month follow up 34% entered CR. Mean survival of the cases was 35.7 months and most of cases were in stage 0,I,II of Rai classification and had received at last 5 cycle of treatment. In this study they claimed that the Fludarabin has had excellent response even in patients who received the drug in second line so encourages to use it in the first line (Stelitano, 1999).

In another study by Halek and Eichhorst in 2004 they evaluated the effect of Fludarabin in combination with other drugs like Cyclphosfamide and because of higher rate of CR and survival it is advised to carry out additional studies of Fludarabin in combination with other agents (Hallek and Eichhorst, 2004).In 2005 a study of 509 CLL cases showed 20% CR rate with Fludarabin in comparison with Chlorambucil, but there was not any significant statistical difference in survival between two regimens. Mean while there was not any difference regarding survival between CAP,CHOP and Fludarabin in the same study ,but serious side effects was more prominent and that is why in CLL patients Chlorambucil is still the drug of choice in first line (No authors listed 2005).Adkins,Markhe and Petters showed that the Fludarabin is equally effective as CAP or CHOP regimen in pretreated patients and comparing with Chlorambucil they had better response and survival . According to their experience Fludarabin is an anti-neoplastic agent that is well tolerated as second line therapy in advanced CLL patients (Adkins et al., 1997). We should take into account that Fludarabin by itself has numerous side effects and myelo suppression is the important dose limiting factor. Other adverse effects of the drug are fever, chills, infection, nausea, vomiting, tiredness, anorexia, fatigue, hemolytic anemia.

Neurotoxicity at lower doses is reversible but sometimes leads to blindness and death. Pulmonary hypersensitivity reaction, stomatitis, macolopapular rash, itching, seborrhea, alopecia, angina pectoris, myalgia, dysuria, hematuria, proteinuria, renal failure and tumor lysis syndrome are in the list of other side effects (Saven and Piro, 1994).

Regarding the wide range of toxic effect of the drug there should be clear indication for using it in treating the patients and risk benefit of its usage should be considered and patients should be informed about it.

As a whole, infection by opportunistic pathogens is the main cause of death in CLL patients (Kalil and Cheson, 2000). Montillo in 1995 in a study that involved 16 cases (11 men and 5 women) of CLL in Binet stage B, C treated with 6 cycle of Fludarabin reported that 4 out of 13 cases who were eligible for study died because of GVHD or infection like as septic shock, meningitis and heart failure (Montillo et al., 1995).In our study 44 out of 126 patients died but there was no specific clue of the reason of their death cause. Just in 2 of them septic shock mentioned to be the cause of death. (The main cause of such unawareness is poor data recording and out of hospital deaths.)

Leporrier's study which is carried out in 2004 with Fludarabin in CLL patients (given in a 5 day every 4 weeks regimen)showed there is significant response both in intermediate risk (stage I,II Rai) and high risk (stage III,IV Rai) patients. Mean survival of the cases was 20-30 months (Leporrier, 2004). Our study stated that most of the patients in stage I, II Rai have achieved PR and those of higher stages had SD or progressive disease. There was no any significant statistical relation between them, that may be because of lower number of cases treated with Fludarabin, but regarding Binet classification this relation showed statistically significant difference between stage and response to treatment.

Regarding lab data and response to treatment patients with better lab tests at presentation had better response to treatment.

As shown in table 1, patients in CR or PR had low WBC and higher Hb , HCT and Plt count at presentation than the patients in PD and SD phase who had significant thrombocytopenia, anemia and higher WBC. This relation has not been evaluated in other studies so we could not get any documentation for our findings or other data to make a statistical analysis.

Poor data recording, unavailability of patients addresses, and not hospitalization in terminal phase in majority of patients caused the paucity of available data and was the major confounding factor.

Conclusion

In the study we ran for evaluating the response to treatment and survival in CLL patients in of Hematology and Oncology Research Center Tabriz University of Medical Sciences, the mean age of 126 cases was 63.7± 8.9. Most of the patients were male. Fatigue was the major complaint at presentation. The majority of the cases were in stage C (Binet) and stage IV(Rai) .Chlorambucil plus Prednisolon was the dominant treatment protocol and most of patients (44.2%) were in PR. As a whole 42 patients

were on Fludarabin with mean (2.6± 1.7) cycle and significant number of them (50%) were in PR and the rest with SD (35%) PD(10%) and CR(5%) .

Mean survival of patients treated with Fludarabin was 43.9± 27.2 month .It was 45±26.5 months for Chlorambucil plus Prednisolone and 50.3± 32.2 months for CVP or CHOP that did not show any significant statistical difference . There was also not any significant relation between survival and kind of response to treatment with Fludarabin .The affects of age, sex, lab findings, complaints at presentation, stage of the disease could not be assessed because of the paucity of the cases and poor medical recording of the patient files, so further evaluation with more cases and good data collection are advised.

References

Adkins JC, Peters DH, Markham A (1997). Fludarabine: An update of its pharmacology and use in the treatment of haematological malignancies. *Drugs*, **53**, 1005-37.

DJ Gibbs S, Westerman D, Lade S, et al (2005). Early B cell chronic lymphocytic leukemia presenting as coetaneous lesions with a normal peripheral blood lymphocyte count. *J Am Acad of Dermatol*, **53**, 534-5.

Hallek M, Eichhorst BF. Chemotherapy combination Treatment regimens with Fludarabine in chronic lymphocytic leukemia. *Hematol J*, **5**, 20-30.

Johnston JB (1998). Chronic lymphocytic leukemia. In: Richard lee G, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM: Wintrobe`s Clinical Hematology. 10thed. vol.2, Canada: Lippincott Williams & Wilkin, 2405-27.

Kalil N, D. Cheson B (2000). Management of chronic lymphocytic leukemia. *Drugs & Aging*, **16**, 9-27.

Kasper DL, Fauci AS, Longo DL, et al (2005). Malignancies of lymphoid cells. In: Armitage JO, Longo DL: Harrison`s principles of internal medicine. 16thed. USA: MacGraw-Hill, 642.

Keating MJ, O`Brien S, Lerner S, et al (1998), editors. Long-term follow up of patients with chronic lymphocytic leukemia (CLL) receiving Fludarabine regimens as initial therapy. *Blood*, **92**, 1165-71.

Lamanna N (2005). Advances in the treatment of chronic lymphocytic leukemia. *Curr Oncol Rep*, **7**, 333-8.

Leporrier M (2004). Role of Fludarabine as monotherapy in the treatment of chronic lymphocytic leukemia. *Hematol J*, **5**, 10-19.

Montillo M, Tedeschi A, Delfini C, et al (1995). Effectiveness of Fludarabine in advanced B-cell chronic lymphocytic leukemia. *Tumori*, **81**, 419-23.

No authors listed (2005). Fludarabine: new indication. First- line treatment of CLL: unconvincing evidence. *Prescrire Int*, **14**, 3-5.

Park DJ, Koeffler HP (2001). Chronic lymphocytic leukemia. In: Haskell CM, Berek JS: Cancer Treatment. 5th ed. USA: WB. Saunders, 1487-96.

Robak T, Kasznicki M (2002). Alkylating agents and nucleoside analogues in the treatment of B-cell chronic lymphocytic leukemia. *Leukemia*, **16**, 1015-27.

Saven A, D.Piro L (1994). 2-Chlorodeoxyadenosine, A Newer purine analog active in the treatment of indolent lymphoid malignancies. *Ann Int Med*, **120**, 784-91.

Stelitano C, Morabito F, Kropp MG, et al (1999). Fludarabine treatment in B-cell chronic lymphocytic leukemia: response, toxicity and survival analysis in 47 cases. *Haematologica*, **84**, 317-23.