Original Article

# Combination therapy of Fludarabine and Cyclophosphamide(FC) Combination Regimen in advance stage of Chronic Lymphocytic Leukemia


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***Summary:***

**Background:** the exposure of chronic lymphocytic leukemia (CLL) cells to fludarabine and cyclophosphamide resulted in an increased, synergistic cytotoxicity . DNA repair mechanisms in CLL cells, which are initiated in response to cyclophosphamide exposition, are inhibited by fludarabine. This observation was later translated into clinical trials evaluating the combination of fludarabine plus cyclophosphamide (FC) showed promising efficacy with response rates exceeding 90% in previously untreated and pretreated patient

**Aim of this study:** To assess the efficacy and safety of combination therapy of fludarabine plus cyclophosphamide in Iraqi adults patients with advance stage of chronic lymphocytic leukemia (CLL) in both previously treated and untreated patients and to assess the treatment free and overall survival in CLL patient who are receiving FC regimen therapy.



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**Patients and methods:** Single arm study was done between February 2005 and fabruary2009.This study included 64 Iraqi patients aged between 39-77years old with advanced stage CLL .All patients received FC combination Therapy(fludarabine25mg/m2 plus cyclophosphamide 250mg/m2 for 3 days intravenously, repeated every 28 days). Treatment was administered for 4-6 courses. Forty eight(75%) patients were treatment naive(N) and 16(25%)were previously treated(Y) with alkylating agent.

**Results:** This combination chemotherapy resulted in 39.1% complete remission rate(CR) and 39.1%partial remission(PR) rate with overall response rated78.2%.The 2years median treatment-free survival was 90% with the median duration of response was 18months. Also there was a significant difference(p value <0.005) between different stage group(C&B) and degree of response, with better response rate in those with stage C than those with stage B, as the overall response rate was 88.3% and 65.5% respectively.

By common toxicity criteria (CTC) grading, the major toxicity(grade 3-4) in patients who treated by FC regimen were nausea and vomiting while the myelosuppression was prominent complication of grade 1&2 as leucopenia and neutropenia occur in 19%, 14% respectively however this is not increased the number of severe infections.

**Conclusion:** Fludarabine and cyclophosphamide combination regimen is an effective therapy for patients with advance CLL with high response and complete remission rate in those untreated and pretreated CLL patients, with good tolerability to this combination.



**Keyword:** Efficiency,Fludarabine,Cyclophosphamide ,Chronic Lymphocytic Leukemia.


## Introduction:

CLL is the classical leukemia of the elderly and the treatment often must be tailored to the patient's fitness level and ability to tolerate more toxic combination therapies. As a consequence, therapy of CLL becomes increasingly personalized, requiring a detailed knowledge about the different diagnostic and therapeutic options(1)Three purine analogues are currently used in CLL:fludarabine, pentostatin, and cladribine. Fludarabine remains by far the best studied compound of the three in CLL ,produces superior overall response (OR) rates compared with other treatment regimens containing alkylating agents or corticosteroids. (2)OR rates of 75–80% and 50%have been reported in treatment- naı¨ve and previously-treated patients respectively.

Complete response (CR) rates with fludarabine monotherapy are typically 15–20% in previously treated patients and 40–50% in treatment-naı¨ve patients.Three randomized trials have shown that the addition of cyclophasphamide to fludrabine clearly improves the CR and OR rate and PFS as compared with fludarabine monotherapy. An additional important result of these trials was that FC did not increase the rate of severe infections despite inducing more grade 3 and 4 neutropenias(3) Fludarabine inhibits the repair of DNA damage caused by


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agents such as Mitoxantrone and cyclophosphamide. A synergistic effect has been demonstrated between fludarabine and cyclophosphamide(4)The major toxicities associated with fludara are neutropenia , noted in approximately two-thirds of treated patients with advanced disease in addition fludarabine produces a pronounced decrease in the number of blood T cells, especially CD4+ T cells, that often persists for more than a year after therapy(5) that apparently lead to increased incidence of infection with opportunistic organisms (6) Other complications that may experienced including reversible neurologic toxicity, even after receiving the standard dose of fludarabine_(6). Increased incidence of new-onset autoimmune diseases, such as autoimmune hemolytic anemia and transfusion-associated graft-versus-host disease,possibly reflecting the overall impairment to the host immune system that is induced by this drug(7)(8).

**Patients and methods:**

This single arm prospective study was carried out in Baghdad teaching hospital and national hematology center in Baghdad between February 2005 to February 2009, to assess the efficacy and tolerability of FC regimen therapy in Iraqi CLL. During this period, 64patients with chronic lymphocytic leukemia in stage B and C according to Benit criteria staging were included, Patients in Binet stage A were excluded.Fourty eight patients were naïve patient while other 16 patients were previously treated with an alkalyting agent. The diagnosis of CLL was done were according to the recommendation of the international workshop of CLL 1989 ( IW-CLL) with Sustained peripheral blood lymphocyte count of $>10x10^9$ \L, most of the cells being mature appearing lymphocyte and bone marrow aspirates showing greater than 30% lymphocyte.Treatment requirement was assessed according to the National Cancer Institute (NCI) criteria. Patients were randomly assigned to receive fludarabine dosed at $25mg/m^2$, administered intravenously daily over 30 minutes for 3days, plus cyclophosphamide$250mg/m^2$ administered intravenously daily over 30 minutes for 3days.This regimen were repeated every 28 days to a maximum of 6 courses. Delaying of therapy for 1-2weeks was permitted if absolute neutrophile count pre course therapy was less than 1500/mm.Response was assessed by peripheral blood sampling, bone marrow aspirate and trephine biopsy after finishing 6 courses of FC regimen. The criteria of response was according to national cancer institute proposal, three types of response were defined: complete response including nodular partial remission, partial response and no response.Complete remission was defined as normal findings on physical examination, disappearance of all symptoms with normal blood count which was defined as lymphocyte count lower than $4 \times 10^9$/L, neutrophil count higher than $1.5 \times 10^9$/L, platelet count higher than $100 \times 10^9$/L, hemoglobin (untransfused) level higher than 110 g/L, and bone marrow lymphocyte percentage less than 30% on aspiration and biopsy. Moreover, imaging diagnostics by chest X-ray and abdominal ultrasound, which had to show negative findings for lymph node enlargement(enlargement was defined as greater than 1cm), splenomegaly and

hepatomegaly. Partial remission was defined as 50% reduction of all measurable disease manifestations in physical and imaging examination and more than 50% improvement of all abnormal blood counts.Non responder was defined as those patients not show regression in lymph nodes, spleen and liver size or improvement in blood counts.Prophylactic therapy were administered from starting point of protocol till 6months after end of last course of therapy and absolute lymphocyte count $\geq 1000/mm^3$.

All data on toxicities were available for only 47patients of 64. Both mild(grades 1 and 2) and severe(grades 3 and 4) side effects were recorded according to CTC criteria.Overall survival was calculated from the randomization time point to death while treatment free survival was calculated from randomization time to the time of disease progression and needs to treatment or death. All data analyzed statistically using SPSS13.

**Results:**

Out of 64patients of CLL with stage B&C who were included in this study, 41(64.1%)patients were male and 23(35.9%) patients were females (M:F ratio1.7:1) with median time follow up of 26months. Age ranged from 39 to 77years with median age 59.9years.Of 64patients of CLL, 48(75%)patients were treatment naïve patients and 16(25%) were previously treated. Stage B disease is seen in 29(45.4%)patients while 35(54.6%) of patients had stage C .

**Table(1) shown patients characteristics**

| | |
|---|---|
| **Age range(median)** | **39 to 77years(59.5)** |
| **Median duration of follow up** | **26 months** |
| **Male:female ratio** | **1.7:1** |
| **Binet staging**<br>**B**<br>**C** | <br>**29(45.4%)**<br>**35(54.6%)** |
| **Treatment naïve patients (untreated)** | **48(75%)** |
| **Pretreated with alkylating agents** | **16(25%)** |

Response state to FC regimen according to NCI-WG criteria shown in table(2) with overall response rate(complete and partial response) was78.2% with median duration of response is 18monthes±11.21.

**Table (2):Degree of remission in different responder patients.**

| Response state | NO. | % |
|---|---|---|
| **Complete response(CR)** | **25** | **39.1%** |
| **Partial response(PR)** | **25** | **39.1%** |
| **No response(NR)** | **14** | **21.9%** |
| **Total** | **64** | **100%** |

The response rate between two different groups of CLL patients showed that higher response rate in untreated than in previously treated patients, 83.4%, 62.5% respectively, with no significant difference between two group ( P value : 0.176) table (3).

**Table(3):Degree of response rate between those previously untreated and treated patients CLL patients.**

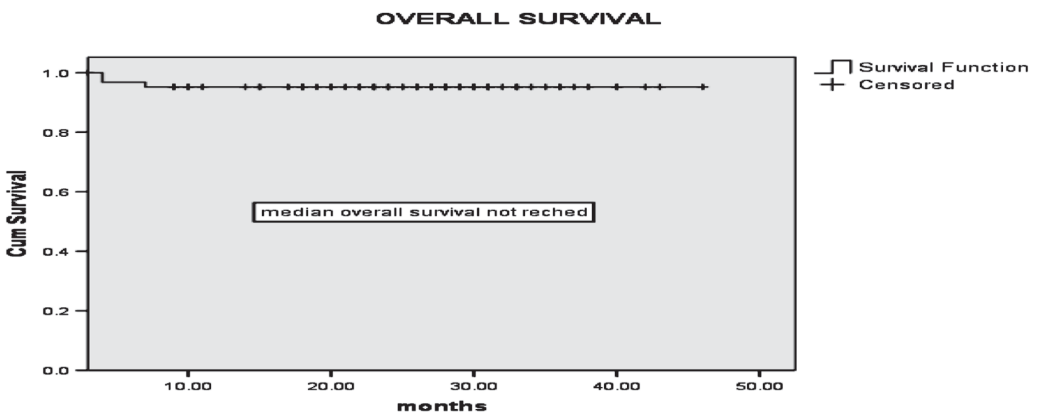
| Type of patients | Degree of response rate | | | Total |
|---|---|---|---|---|
| | CR | PR | NR | |
| Previously untreated | 21(43.8%) | 19(39.6%) | 8(16.7%) | 48 |
| Previously treated | 4(25%) | 6(37.5%) | 6(37.5%) | 16 |

While significant difference (P value 0.005) was found in the overall response rate among different stages of CLL patients was shown to be higher with(88.5%) among group C patients than among group B CLL patients(65.5%), the CR rate was prominently higher for stage B than C as table( 4)shown.

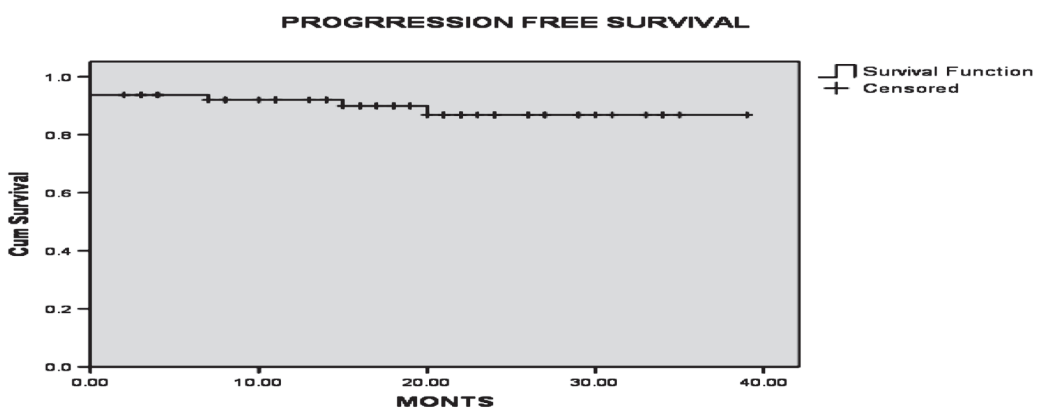
**Table(4):Patients differences between response rate and different CLL stages.**

| stage of CLL | State of response | | | Total |
|---|---|---|---|---|
| | CR | PR | NR | |
| B | 14(48.3%) | 5(17.2%) | 10(34.5%) | 29(100%) |
| C | 11(31.4%) | 20(57.1%) | 4(11.4%) | 35(100%) |

Only 4(6.2%) patients who died during the study, three of them due to sever disseminated infections while the other one died because of failure response to FC regimen due to cerebral hemorrhage because of sever thrombocytopenia.
Overall survival of these patients with median duration of follow up of 26 months was about 95% within 2years




**Figure(1):Overall survival for all patients**
Three patients(4.6%) had been relapsed within 2years with treatment free survival of 90%.




**Figure(2):Progression free survival of all patients**
Incidence of FC regimen induced toxicity in these patients was recorded in 47CLL patients as shown in table (7).

**Table(5): undesirable side effect of FC regimen in CLL patients.**

| UNDESIRABLE EFFECT | Grade 1-2 (no.) | % | Grade 2-3 (no.) | % |
|---|---|---|---|---|
| General condition | 30 | 63.8 | 14 | 29.7 |
| Anemia | 38 | 80.8 | 14 | 19.1 |
| leucopenia | 21 | 44.6 | 7 | 14.8 |
| neutropenia | 23 | 48.9 | - | - |
| infection | 39 | 82.9 | 8 | 17.02 |
| Fever | 28 | 59.5 | 19 | 40.4 |
| nausea | 7 | 14.8 | 40 | 85.1 |
| vomiting | 1 | 2.1 | - | - |
| stomititis | 15 | 31.9 | 20 | 42.5 |
| diarrhea | 6 | 12.7 | - | - |
| bilirubin | 0 | 0 | 2 | 4.2 |
| SGOT/SGPT | 0 | 0 | 2 | 4.2 |
| Peripheral neuropathy | 9 | 6.3 | - | - |

**Discussion:**

The nucleoside analogue, fludarabine, is very effective drugs in the treatment of CLL, This efficacy has been demonstrated in several studies with higher remission rate than conventional chemotherapy in advanced CLL, particularly in patient resistant to alkylating agent(9).The FC regimen response showed overall response rate 78.2% with complete response in 39 %without significant difference in response rate among those previously treated and untreated patients(p-value 0.176). This response had been shown by multicenter phase III study initiated by ECOG with response rate to combination therapy in 74.3% and complete response23.4%(10).Similarly German CLL phase II study group evaluated the efficacy and toxicity of a combination of fludarabine and cyclophosphamide (FC) in patients with B-cell CLL in 36 patients with overall response rate(RR) 90·6%, with 13·9%complete remission( CR) and 66·6% partial remission (PR) with high response rate of the FC regimen was independent of the treatment status prior to the study. The separate analysis of response for untreated and pretreated patients revealed no significant difference, with a response rate of 85·7 and 94·4% respectively(9). The German CLL group phase III study by Eichhorst et al also yields higher response rate 94%,and similar CR 24% to U.S intergroup.(11). The effectiveness of this combination translated in this study in advance stage with significant difference(p value0.02) in response rate between two different stages of CLL(stage B&C) where 88.3% of patients with stage C had response (partial and complete response) and 65.5% of stage (B )were experience this response and this is comparable to German CLL Study Group results which showed benefit of CLL patients with stage C disease more from stage B patients who used FC regimen than from fludarabine monotherapy(11). The effectiveness of this combination extended to those previously treated with different type of alkylating agents,with response not different from those naïve patients.Susan M. O'Brien etal showed that Fludarabine and cyclophosphamide produced 80% response rates in all patients not refractory to fludarabine at the start of therapy as well as a 38% response rate in patients who were refractory to fludarabine. The complete remission (CR) rate was 35% in previously untreated patients, which was not significantly different from the CR rate in historical control patients treated with single-agent fludarabine(6).Only 4(6.25%)patients enrolled in this study died before completing their courses of therapy and regarded as failure of induction of response, all deaths were of stage C and previously heavily treated CLL patients, the cause of death was sever infection in 3patients and intracerebral hemorrhage in the 4$^{th}$ one.The median observation time of 26 months was too short to validate a survival difference between pretreated and untreated patients withTwo-year overall survival is currently estimated as 95% for patients randomly assigned to FC.Toxicity data were available only in 47patients.Non hemopoietic toxicity recorded in 85% of patients who experienced grade 3-4 toxicity nausea and this may be due to our under treatment of patients with antiemetic. Non serious infection of grade 1-2 toxicity was shown in 82.9% and 42.5% had experience grade 3 – 4 toxicity with oral cavity infections. Anemia and neutropenia was mostly of grade 1 and 2 toxicity in 80.8%, 48.9% respectively.This low incidence of myelossupprssion may be due to lower dose of cyclophosphamide which had been used by other studies.Hallek .etal. Interestingly, showed that no severe infection (CTC grade 3 and 4) was observed, despite the frequent occurrence of CTC grade 3 and 4 neutropenia in more than two-thirds of patients(69.4%)(9).Again Eichhorst et al with FC therapy caused thrombocytopenia in15.6% and leukocytopenia in 55.5%, but did not increase the number of severe infection(11). in summery FC combination is effective therapy in Iraqi adult CLL whether patient untreated or pretreated previously with side effects that not different from other studies.

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