Long term survival after FCR treatment in previously untreated chronic lymphocytic leukemia patients

written by;
Shokhan Muhammad, Ahmed Yassin
Nanakaly cancer center /Iraq

Abstract

Background: Chronic lymphocytic leukemia (CLL) is characterized by a lower incidence rate in Iraq and Kurdistan as compared to Western countries. However, a good prognosis of chronic lymphocytic leukemia is dependable on diagnosis, risk stratification, and a better choice of an appropriate treatment regimen.
Aim of the study: To evaluate the effectiveness of fludarabine, cyclophosphamide, and rituximab (FCR) regimen in comparison to other chemotherapy regimens in the management of patients with chronic lymphocytic leukemia in Kurdistan region/Iraq.
Patients & Methods: A retrospective cross-sectional review study carried out in three cancer centers in Kurdistan region of Iraq for the duration of ten years through the period from 1st of January, 2010 to 31st of December, 2019 on a convenient sample of 152 CLL patients. Diagnosis of CLL was done by the hematologist in Kurdistan cancer centers according to the International Workshop on Chronic Lymphocytic Leukemia. The treatment of CLL patients was either by FCR chemo-immunotherapy regimen or other chemotherapies like BR.
Results: The FCR chemo-immunotherapy was the treatment of 38.8% of CLL patients, while 61.2% of CLL patients were treated by other chemotherapies. There was a significant association between younger age patients and FCR chemo-immunotherapy (p=0.001). There was a significant association between a complete response for those patients who were treated by FCR chemo-immunotherapy (p=0.02). The mean survival duration and progression free survival of CLL patients treated by FCR chemo-immunotherapy was significantly longer than the mean survival duration of CLL patients treated by other chemotherapies (p=0.01).
Conclusions: Complete response and survival of CLL patients treated by FCR chemo-immunotherapy were better than the complete response and survival of CLL patients treated by other chemotherapies.

Background

The treatment regimens of CLL include a combination of chemotherapy and immunotherapy or drugs that target the signaling pathways. The monotherapy with alkylating agents was considered as the front-line therapy for CLL for many previous decades, they are indicated for palliation therapy in elderly patients. [9] Other treatment regimens are chemoimmunotherapy using monoclonal antibodies (anti-CD20 antibodies like rituximab, ofatumumab, and obinutuzumab) with chemotherapy, agents targeting the signaling in CLL cells and their environment, and BCL-2 inhibitor.[3]
Chemo-immunotherapy using a regimen of fludarabine, cyclophosphamide, and rituximab (FCR) had shown an improvement of the outcomes for patients with poor prognosis especially if given at an early stage of CLL.[10] The FCR was the first treatment regimen of CLL that revealed a longer survival duration of patients with advanced-stage CLL and recently, it is regarded as the standard management choice and first-line therapy for patients with appropriate physical fitness.[11-15] Although higher efficacy of FCR in the treatment of, this regimen is accompanied by relapses and drug toxicity (febrile neutropenia, hematological toxicity, etc.).

In Iraq, due to economic and frequent wars and disasters affecting the national health system, the oral alkylating agent was the treatment option in the management of CLL for the last several decades.[17] Nowadays, the treatment regimens using rituximab were administered increasingly for Iraqi patients with better outcomes of CLL.[18] The high cost of FCR and difficulties in acquiring this treatment by patients, in addition to reported toxicity, all of these urged us to conduct this study which aimed to evaluate the effectiveness of FCR treatment regimen in comparison to other chemotherapy regimens in the management of patients with CLL in Kurdistan region/Iraq.

Materials & Methods

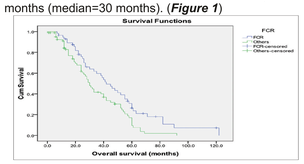
The design of this current study was a retrospective cross-sectional review study carried out in 3 cancer centers in Kurdistan region. The duration of the study was ten years through the period from 1st of January, 2010 to 31st of December, 2019. The study population was the review of data for all chronic lymphocytic leukemia patients admitted to three cancer centers in Kurdistan region (Nanakaly Hospital in Erbil city, Hiwa hospital in Sulaymaniyah city and Azadi center in Duhok city). The inclusion criteria included patients with CLL from all age groups, previously untreated, diagnosed by flow cytometry or bone marrow biopsy with IHC who completed at least three cycles of FCR and BR or other chemotherapies. The exclusion criteria were patients not completed the treatment cycles, disease duration of less than one year, patients were not treated, patients refused treatment, missed data, and the presence of active disease in patients with Binet stage A and B. The ethical considerations were implemented according to Helsinki Declaration regarding ethical approval of Health authorities, ethical approval was taken from Kurdistan Board Ethical Committee, and confidentiality of data. A convenient sample of 152 CLL patients was selected after eligibility to inclusion and exclusion criteria.
The data were collected by the researcher from saved records of CLL patients in three cancer centers and some information was collected directly from patients and fulfilling a prepared questionnaire. The questionnaire was designed by the researcher. The chemotherapy treatment of studied CLL patients was Chlorambucil alkylating agent, rituximab anti-CD20 monoclonal antibody, BR (Bendamustine an alkylating agent and rituximab. Also, Ibrutinib, a Bruton kinase inhibitor as oral administration, Idelalisib PI3K inhibitor, and other chemotherapy lines like RCHOP. The dose of FCR for selected CLL patients was (fludarabine 25 mg /m^2 day 1 to 3), (Cyclophosphamide 250 mg /m^2 day 1 to 3) and (Rituximab 375 mg per m^2 for day 1 only from each cycle) for 6 cycles repeated every 28 days. The adverse effects of FCR were collected from data of CLL patients.
The dose of Bendamustine Rituximab was (B 90mg/m^2 i.v day 1+2, R 375 mg/m^2 i.v day 1 all subsequent courses; q 28 days).
The age of CLL patients was categorized into five groups and ranged from 25 years to 94 years. The residence of CLL patients was distributed into three cities of Kurdistan Region.
The data collected were analyzed statistically by Statistical Package of Social Sciences software version 22. The Chi-square and Fischer's exact tests were applied for analyzing the data as suitable. Kaplan-Meier curve was used to assess the survival duration of CLL patients. The level of significance (p-value) was regarded statistically significant if it was 0.05 or less.

Table 1: General characteristics of CLL patients.

Variable	No.	%
Age mean±SD (65.9±12.5 years)		
<50 years	16	10.5
50-59 years	28	18.4
60-69 years	51	33.6
70-79 years	32	21.1
≥80 years	25	16.4
Gender		
Male	109	71.7
Female	43	28.3
Binet stage		
Stage A	49	32.2
Stage B	47	30.9
Stage C	56	36.8
Rai staging		
Stage 0	22	14.6
Stage I	19	12.6
Stage II	44	29.1
Stage III	21	13.9
Stage IV	45	29.8
Total	152	100.0

Results

This study included 152 patients with (CLL) with a mean age of (65.9 years) and range of 25-94 years. Male CLL patients were more than females with a male to female ratio of 2.5:1. The Binet stage of CLL patients was distributed as follows; stage A (32.2%), stage B (30.9%), and stage C (36.8%). Treatment cycles were (5.2 cycles); 62.5% of CLL patients received 6 cycles and more of chemotherapy treatment. The treatment response of CLL patients was complete response (51.3%), partial response (21.1%), stable (12.5%), no response (13.8%) and progressive (1.3%). The current status of CLL patients was either dead (23%), or alive (77%).
The mean survival of CLL patients was (36.1 months); 78.9% of CLL patients had a survival of less than 5 years and 21.1% of CLL patients had a survival of 5 years and more. There was a significant association between younger age CLL patients and FCR chemo-immunotherapy (p=0.001). No significant differences were observed between CLL patients treated by FCR and CLL patients treated by other chemotherapies regarding gender (p=0.1), residence (p=0.6), Binet stages (p=0.09), and Rai staging (p=0.1).
There was a significant association between a complete response and CLL patients treated by FCR chemo-immunotherapy (p=0.02). The mean survival duration of CLL patients treated by FCR chemo-immunotherapy was significantly longer than the mean survival duration of CLL patients treated by other chemotherapies (p=0.01).
The overall mean survival of all treated CLL patients was 40.6 months (median=35 months), the overall mean survival of CLL patients treated by FCR chemo-immunotherapy was 48.4 months (median=42 months), while the overall mean survival of CLL patients treated by other chemotherapies was 34.7 months (median=30 months). (***Figure 1***)



Regarding FCR as compared to BR (Bendamustine Rituximab) , 44 patients received first line treatment with BR, No significant differences were observed between CLL patients treated by FCR and CLL patients treated by BR regarding treatment cycles (p=0.4) and current status (p=0.8).
The mean progression-free survival (PFS of CLL patients treated by FCR chemo-immunotherapy) was 35 months and the mean survival duration was 48.4 months. The mean progression-free survival (PFS) of CLL patients treated by BR was 23.7 months and The mean survival duration was 34.8 months and (p=0.002). (***Table 5***)



Figure 2 : Kaplan-Meier curve of CLL patients (blue=FCR), (red=BR).

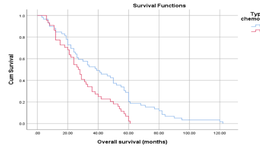


Figure 3 : Kaplan-Meier curve of CLL patients (blue=FCR), (red=BR).

Summary

Complete response and survival of CLL patients treated by FCR were better than complete response and survival of patients treated by other chemotherapies. This study recommended more efforts from national health authorities to enforce the treatment supplies of health centers in the Kurdistan region and Iraq with FCR and encourage physicians to use it as first-line treatment of CLL patients. Further randomized controlled trials on the efficacy and safety of FCR in the treatment of CLL must be supported.

Acknowledgment
Great thanks to all medical health staff working in cancer centers in Kurdistan for their efforts and help to complete my research.

Discussion

In the present study, 38.8% of studied CLL patients in Kurdistan were treated by FCR chemo-immunotherapy. This finding is better than the results of a previous study carried out in Erbil city which reported that 22.9% of CLL patients were treated by FCR [22].
The treatment response for all chemotherapy treatment types in our study was commonly a complete response (51.3%). This finding is close to the results of Nazir et al [23] study in Pakistan on 57 patients with CLL which found that 56% of CLL patients had a complete response after chemo-immunotherapy
The current study showed a significant association between a complete response and CLL patients treated with FCR chemo-immunotherapy (p=0.02), 66% of CLL patients treated with FCR had a complete response.
This finding is close to the results of many literatures such as Hallek et al [13] studies in Germany which compare the FCR treatment for 408 CLL patients with 409 CLL patients treated by chemotherapy (FC) and found that complete response in the FCR group (65%) that was significantly higher than complete response (45%) of FC group and Tam et al [14] studies in USA which found after follow up of 6 years for CLL patients treated by FCR, the complete response was 72%.
In the current study, there was a significant association between younger age CLL patients and FCR chemo-immunotherapy treatment (p=0.001). This finding coincides with the results of Xu et al [21] study in China which reported better treatment response and survival for younger CLL patients than elderly age CLL patients.
Generally, the five years survival rate of treated CLL patients in the current study was (21.1%) and 23% of CLL patients have died.
This finding is different from the results of the Hasan study in Erbil which found that five years survival rate of CLL patients was (67.7%) and 32.4% of CLL patients died [22]. This difference might be attributed to fact that the previous Iraqi study included treated and untreated CLL patients and our study included CLL patients not completing five years follow-up period.
The present study also compared FCR with BR , and it showed that the mean PFS duration of CLL patients treated by FCR was significantly longer than the mean PFS of CLL patients treated by BR as first line treatment (p=0.001) .These findings are in agreement with the results of Eichhorst et al study in Germany on 561 CLL patients which found longer mean PFS of patients treated by FCR as compared to patients treated by BR.

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