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

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Abstract

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
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

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

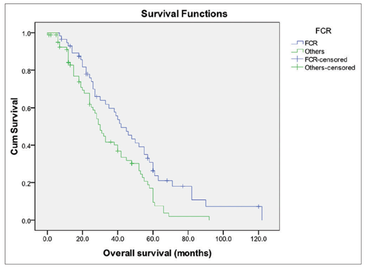
The design of this current study was a retrospective cross-sectional review study carried out in cancer centers in Kurdistan region. The duration of the study was ten years through the period from 1st of January, 2010 to 31st of December, 2019. The study population was the review of data for all chronic 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 chronic lymphocytic leukemia from all age groups, previously untreated, diagnosed by flow cytometry or bone marrow biopsy with immunohistochemistry 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.

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

Rsults

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). 4 patients with Rai stage 0 have received FCR chemotherapy later in their course of illness due to progressive disease, development of B symptoms or immune cytopenia
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).

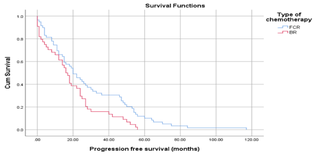


Figure 2 ... Kaplan-Meier curve of CLL patients (blue=FCR), (red=BR).

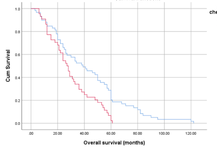


Figure 3... Kaplan-Meier curve of CLL patients (blue=FCR), (red=BR).

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.

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%).
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.
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 [31] study in China which reported better treatment response and survival for younger CLL patients than elderly age CLL patients. Generally, the five years survival ate of treated CLL patients in the current study was (21.1%) and 23% of CLL patients have died.

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