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Long-term survival after fludarabine, cyclophosphamide, and rituximab treatment in previously untreated chronic lymphocytic leukemia patients

Shokhan Mohammad Mustafa, Ahmed Khudair Yassin, Nawsherwan S. Mohammed[1], Rawand P. Shamoon[1], Marwa N. Karam, Shlan S. Mohammad, Lara Lateef Abdulrahman, Zhalla O. Ahmed[2], Bryar Sabah Rashid[2], Tavan I. Mahmood[2], Rozhhat A. Yousif[3], Kawa M. Hasan[4], Zeki A. Mohamed[5], Hisham A. Getta[6], Sana D. Jalal[6], Dana A. Abdullah[6], Basil K. Abdulla[7], Ghanim S Numan[8], Ranan Karadagh[2]

Department of Clinical Hematology, Nanakaly Hospital for Blood Disease, Departments of [1]Pathology and [4]Medicine, College of Medicine, Hawler Medical University, Erbil, [2]Department of Cnical Hematology, Hiwa Hospital for Blood Disease, [6]Department of Pathology, College of Medicine, University of Sulaymaniyah, [7]Department of Hematology, Hiwa Cancer hospital, Sulaymaniyah, [3]Azadi Centre for Blood Disease, [5]Department of Medicine, College of Medicine, University of Duhok, Duhok, Kurdistan Region, [8]Department of Clinical Hematology, Nanakaly Hospital for Blood Disease, Erbil, Iraq

Address for correspondence:
Dr. Shokhan Mohammad Mustafa, Nanakaly Hospital for Blood Disease, Erbil, Kurdistan Region, Iraq.
E-mail: shokhan.mohammad@yahoo.com

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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 CLL 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 CLL in Kurdistan region/Iraq.

PATIENTS AND METHODS: A retrospective review study carried out in three cancer centers in the Kurdistan region of Iraq for the duration of 10 years through the period from January 1, 2010 to December 31, 2019, on 152 CLL patients. CLL was diagnosed according to the International Workshop on CLL. The treatment of CLL patients was either by FCR chemo-immunotherapy regimen or other chemotherapies.

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 the use FCR chemo-immunotherapy ($P = 0.001$). There was a significant association between a complete response and treatment by FCR chemo-immunotherapy ($P = 0.02$). The mean overall survival duration and progression-free survival of CLL patients treated by FCR chemo-immunotherapy were significantly longer than the mean survival time 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.

Keywords:

And rituximab, chronic lymphocytic leukemia, complete response, cyclophosphamide, fludarabine, survival

Introduction

Chronic lymphocytic leukemia (CLL) is defined as malignancy of CD5$^+$ B-cells and specified that is characterized by the aggregation of small and matured appearance of neoplastic lymphocytes in the blood, bone marrow, and secondary lymphoid tissues leading to

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lymphocytosis, lymphadenopathy, and splenomegaly. Epidemiologically, the prevalence of CLL is high among the western population and lower among the Asian population.[1] In Iraq, CLL is an infrequent type of leukemia with a lower incidence rate.[2]

Diagnosis of CLL depends mainly on the count of B-lymphocytes in peripheral blood and is confirmed by flow cytometry.[3] The World Health Organization defines CLL as lymphocytic lymphoma that is recognized from small lymphocytic lymphoma through the appearance of leukemia.[4] For purpose of risk stratification, staging, and prognosis, the Rai and Binet staging systems were developed which are characterized by simplicity, low cost, and dependability on clinical parameters and laboratory investigations.[5,6]

In general, the common indications for treatment of CLL are anemia and thrombocytopenia, symptomatic lymphadenopathy, and/or other symptoms related to active disease. For CLL patients at early stages (Rai Stages I or Stage II, or Binet Stages A or Stage B), the therapy is not recommended, unless the disease is progressed or accompanied by severe symptoms. Markers of CLL disease progression are double lymphocyte count in <1 year, lymphadenopathy, and/or splenomegaly.[7] This choice of clinical observation without intervention watch and wait is commonly considered for the treatment of early-stage CLL and depends mainly on recurrent failed previous attempts to acquire management of CLL patients by early treatment.[8,9]

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.).[16]

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.

Patients and Methods

The design of this current study was a retrospective review study carried out in cancer centers in the Kurdistan region. The duration of the study was 10 years through the period from January 1, 2010 to December 31, 2019. The study population was the review of data for all CLL patients admitted to three cancer centers in the 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 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 <1 year, patients were not treated, patients refused treatment, missed data. The ethical considerations were implemented according to Helsinki Declaration regarding ethical approval of Health authorities, ethical approval was taken from the Kurdistan Board Ethical Committee and confidentiality of data. After meeting the inclusion and exclusion criteria, a suitable sample of 152 CLL patients was chosen.

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 questionnaire included the following: General characteristics of CLL patients (age, gender, residence, Binet stage, and Rai staging) treatment characteristics (treatment type and treatment cycles), and outcome (treatment response, current status, and survival duration). Diagnosis of CLL was made by the hematologist in Kurdistan cancer centers according to the International Workshop on CLL (iwCLL).[19] The decision of treatments was made by the senior in charge. The chemotherapy treatment of studied CLL patients was Chlorambucil, rituximab 375 mg\m^2, BR (Bendamustine 100 mg\m^2 i. v day 1 + 2, and rituximab 375 mg\m^2 day 1 q 28 days). Furthermore, Ibrutinib, a Bruton kinase inhibitor

420 mg daily as oral administration, Idelalisib PI3K inhibitor 150 mg twice daily, and other chemotherapy lines like RCHOP. The dose of FCR for selected CLL patients was (fludarabine 25 mg/m^2 day 1–3), (Cyclophosphamide 250 mg/m^2 day 1–3), and (Rituximab 375 mg/m^2 for day 1 only from each cycle) for six cycles repeated every 28 days. The adverse effects of FCR were collected from data of CLL patients.

Clinical examination and investigative findings were used to determine the Binet and Rai staging of CLL patients.[5,6] The treatment response was assessed according to iwCLL[19] into five categories (complete response, partial response, stable, no response, and progressive). The researcher evaluated the death and living outcomes. The survival time of CLL patients was calculated based on the length of follow-up.

The data collected were analyzed statistically by the Statistical Package for the 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.

Results

This study included 152 patients with CLL with a mean age of 65.9 years and range of 25–94 years; 10.5% of patients were in age group <50 years, 18.4% of them were in the age group 50–59 years, 33.6% of them were in the age group 60–69 years, 21.1% of them were in the age group 70–79 years and 16.4% of them were in the age group of 80 years and more. 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%). Rai staging of CLL patients was Stage 0 in 14.6% of them, Stage I in 12.6% of them, Stage II in 29.1% of them, Stage III in 13.9% of them, and Stage IV in 29.8% of them [Table 1].

The FCR chemo-immunotherapy was the treatment of 38.8% of CLL patients, while 61.2% of CLL patients were treated by other chemotherapies. Mean chemotherapy treatment cycles were (5.2 cycles); 62.5% of CLL patients received six 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 <5 years and 21.1% of CLL patients had a survival of 5 years and more [Table 2].

Table 1: General characteristics of chronic lymphocytic leukemia patients

Variable	*n* (%)
Age mean±SD (65.9±12.5 years)	
<50	16 (10.5)
50-59	28 (18.4)
60-69	51 (33.6)
70-79	32 (21.1)
≥80	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)

*Early-stage CLL patients usually do not receive treatment unless they are progressed. CLL=Chronic lymphocytic leukemia, SD=Standard deviation

Table 2: Chemotherapy treatment and outcomes of chronic lymphocytic leukemia patients

Variable	*n* (%)
Treatment	
FCR	59 (38.8)
Other chemotherapies	93 (61.2)
Treatment cycles mean±SD (5.2±2 cycles)	
<6	57 (37.5)
≥6	95 (62.5)
Treatment response	
Complete response	78 (51.3)
Partial response	32 (21.1)
Stable	19 (12.5)
No response	21 (13.8)
Progressive	2 (1.3)
Status	
Dead	35 (23.0)
alive	117 (77.0)
Survival mean±SD (36.1±24.9 months)	
<60	120 (78.9)
≥60	32 (21.1)
Total	152 (100.0)

FCR=Fludarabine, cyclophosphamide, and rituximab, SD=Standard deviation

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 ($P = 0.1$). Along with other disease stages who received treatment, 4 patients with Rai stage 0 have

received FCR chemotherapy later in their course of disease due to progressive disease, development of B symptoms, or immune cytopenia [Table 3].

No significant differences were observed between CLL patients treated by FCR and CLL patients treated by other chemotherapies regarding treatment cycles ($P = 0.4$) and current status ($P = 0.8$). 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 ($P = 0.01$) [Table 4].

The mean overall survival of all treated CLL patients was 40.6 months (median = 35 months), the mean overall survival of CLL patients treated by FCR chemo-immunotherapy was 48.4 months (median = 42 months), while the mean overall 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 overall survival duration was 48.4 months. The mean PFS of CLL patients treated by BR was 23.7 months and The mean overall survival duration was 34.8 months and ($P = 0.002$) [Table 5].

The PFS and the mean survival duration and of CLL patients treated by FCR chemo-immunotherapy were significantly longer than the mean survival duration and PFS of CLL patients treated by BR. Figures 2 and 3.

The adverse effects of FCR chemo-immunotherapy of CLL patients were positive among 47.5% of CLL patients; hematotoxicity like grade 3 and 4 anemia and thrombocytopenia requiring platelet and blood transfusion was shown among 20.3% of CLL patients and febrile neutropenia was shown among 44.1% of them, while the secondary malignancies were present in one CLL patient only [Table 6].

Table 3: Distribution of chronic lymphocytic leukemia patients' general characteristics according to chemotherapy treatment type

Variable	Treatment		*P*
	FCR, *n* (%)	Others *n* (%)	
Age (years)			
<50	10 (16.9)	6 (6.5)	0.001 (S)
50-59	16 (27.1)	12 (12.9)	
60-69	22 (37.3)	29 (31.2)	
70-79	9 (15.3)	23 (24.7)	
≥80	2 (3.4)	23 (24.7)	
Gender			
Male	46 (78.0)	63 (67.7)	0.1 (NS)
Female	13 (22.0)	30 (32.3)	
Binet stage			
Stage A	13 (22.0)	36 (38.7)	0.09 (NS)
Stage B	20 (33.9)	27 (29.0)	
Stage C	26 (44.1)	30 (32.3)	
Rai staging			
Stage 0	4 (6.9)	18 (19.4)	0.1 (NS)
Stage I	10 (17.2)	9 (9.7)	
Stage II	15 (25.9)	29 (31.2)	
Stage III	9 (15.5)	12 (12.9)	
Stage IV	20 (34.5)	25 (26.9)	

S=Significant, NS=Not significant, FCR=Fludarabine, cyclophosphamide, and rituximab

Table 4: Distribution of chronic lymphocytic leukemia patients' treatment and outcomes according to chemotherapy treatment type

Variable	Treatment		*P*
	FCR, *n* (%)	Others, *n* (%)	
Treatment cycles (cycles)			
<6	20 (33.9)	37 (39.8)	0.4 (NS)
≥6	39 (66.1)	56 (60.2)	
Treatment response			
Complete response	39 (66.1)	39 (41.9)	0.02 (S)
Partial response	12 (20.3)	20 (21.5)	
Stable	3 (5.1)	16 (17.2)	
No response	5 (8.5)	16 (17.2)	
Progressive	0	2 (2.2)	
Status			
Dead	13 (22.0)	22 (23.7)	0.8 (NS)
Alive	46 (78.0)	71 (76.3)	
Survival			
Mean±SD (months)	42.5±26.4	31.9±23.1	0.01 (S)

S=Significant, NS=Not significant, SD=Standard deviation, FCR=Fludarabine, cyclophosphamide, and rituximab

Discussion

Chemo-immunotherapy is regarded recently and in the future as a common amelioration in the management of CLL. The risk stratification of CLL patients is essential in improving the efficacy of treatment and the prognosis. It was shown that earlier treatment of earlier stage asymptomatic CLL patients is not beneficial and may be accompanied by higher rates of drug toxicity with no effect on the survival of those patients.[19,20]

In the present study, 38.8% of studied CLL patients in Kurdistan were treated by FCR chemo-immunotherapy. This finding is different than the results of a previous study carried out in Erbil city which reported that 22.9% of CLL patients were treated by FCR.[21] The

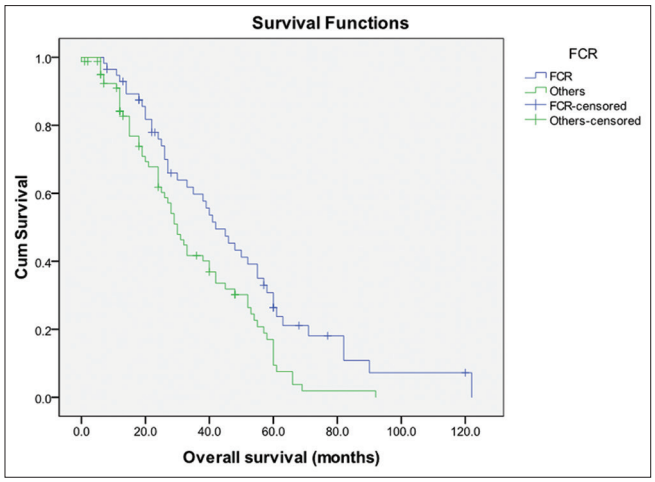

Figure 1: Kaplan-Meier curve of chronic lymphocytic leukemia patients (blue = Fludarabine, cyclophosphamide, and rituximab), (green = other chemotherapies)

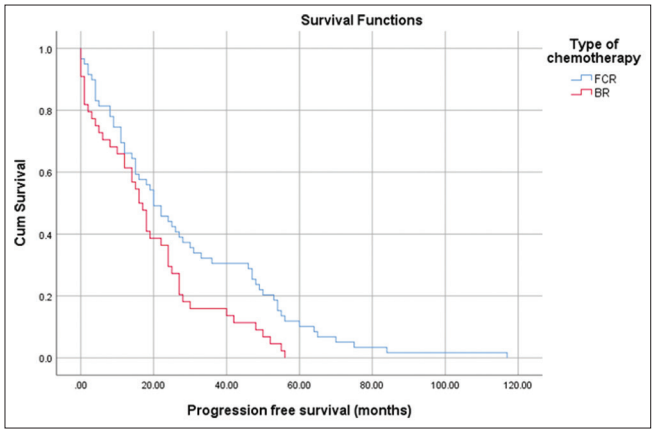

Figure 2: Kaplan-Meier curve of chronic lymphocytic leukemia patients (blue = Fludarabine, cyclophosphamide, and rituximab), (red = BR)

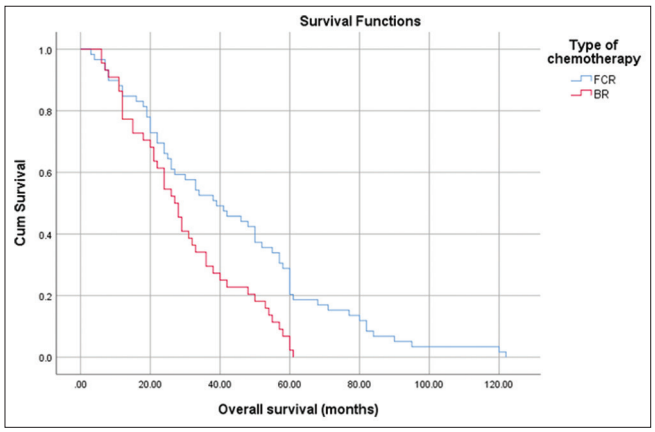

Figure 3: Kaplan-Meier curve of chronic lymphocytic leukemia patients (blue = Fludarabine, cyclophosphamide, and rituximab), (red = BR)

FCR is effective chemo-immunotherapy but with a high cost that is not affordable by all CLL patients, in addition to the presence of contraindications and good alternatives. The treatment response for all chemotherapy

Table 5: Distribution of chronic lymphocytic leukemia patients' treatment and outcomes according to chemotherapy treatment type. fludarabine, cyclophosphamide, and rituximab and bendamustine rituximab

Variable	Treatment		*P*
	FCR, *n* (%)	BR, *n* (%)	
Treatment (cycles)			
<6	20 (33.9)	12 (27.3)	0.4 7 (NS)
≥6	39 (66.1)	32 (72.7)	
Status			
Dead	13 (22.0)	4.0 (9.1)	0.8 (NS)
Alive	46 (78.0)	40 (90.9)	
Overall survival	48.4	34.8	0.002 (S)
Progression free survival	35.0	23.7	
Mean±SD (months)	42.5±26.4	29.8±16.9	0.001 (S)

S=Significant, NS=Not significant, FCR=Fludarabine, cyclophosphamide, and rituximab

Table 6: Adverse effects of fludarabine, cyclophosphamide, and rituximab

Variable	*n* (%)
Adverse effects of FCR	
No	31 (52.5)
Yes	28 (47.5)
Hematotoxicity	
No	47 (79.7)
Yes	12 (20.3)
Febrile neutropenia	
No	33 (55.9)
Yes	26 (44.1)
Secondary malignancies	
No	58 (98.3)
Yes	1 (1.7)
Total	152 (100.0)

FCR=Fludarabine, cyclophosphamide, and rituximab

treatment types in our study was commonly a complete response (51.3%). This finding is close to the results of Nazir *et al*.[22] 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*.[12] studies in Germany (phase 3 trial) 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*.[13] studies in the USA which found after follow-up of 6 years for CLL patients treated by FCR, the complete response was 72%. In a more recent randomized prospective phase, 3 study conducted by Herling *et al*.[10] in Germany on 201 patients with Binet stage A high-risk CLL found that complete response of

selected CLL patients treated by FCR for three cycles and more reached (81.3%). Recently, two trials had also shown good outcomes of FCR in special subgroups of CLL patients like mutated IGVH, del (13q), trisomy 12, or del (11q), or those patients achieving a minimal residual disease negative remission.[23,24]

In general, the 5 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 5 years survival rate of CLL patients was (67.7%) and 32.4% of CLL patients died.[21] 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 5 years follow-up period. The present study also compared FCR with BR, as BR was among the first line of therapy after FCR and it showed that the mean PFS duration and of CLL patients treated by FCR chemo-immunotherapy was significantly longer than the mean PFS of CLL patients treated by Bendamustine and Rituximab as first-line treatment (P = 0.001) These findings are in agreement with the results of Eichhorst *et al*.[25] study in Germany on 561 CLL patients (282 patients treated by FCR and 279 patients treated by bendamustine and rituximab) which found longer mean survival of patients treated by FCR as compared to patients treated by bendamustine and rituximab. Similarly, both Keating *et al*.[11] studies in the USA and Thompson *et al*.[23] studies in Australia revealed longer overall survival of CLL patients as compared to other chemotherapies. Fischer *et al*.[24] reported a PFS With a median follow-up of 5.9 years, median PFS was 56.8 in the FCR group and a longer survival of more than 10 years for CLL patients with mutated IGHV after treatment by FCR. The Kaplan-Meier curve in the present study showed that the overall mean survival of CLL patients treated by FCR was 48.4 months, while the overall mean survival of CLL patients treated by other chemotherapies was 34.7 months.

The Kaplan–Meier curve also showed mean PFS of CLL patients treated by FCR was 35 months, while the mean PFS of CLL patients treated by BR was 23.7 months.

Although this higher rates of complete remission and longer survival of patients treated with FCR in the present study, the adverse effects of FCR chemo-immunotherapy of CLL patients was positive among 47.5% of CLL patients; febrile neutropenia (44.1%), hematotoxicity (20.3%) and secondary malignancies (1.7%). These findings are consistent with the results of many previous literatures.[25,26,27] In addition to the adverse effects of the FCR regimen, several obstacles facing the choice of FCR in treatment of CLL like physical intolerance of CLL patients to six cycles of FCR chemo-immunotherapy, intolerance of elderly age, and lower outcomes in subgroups of CLL patients.[28] Foon *et al*.[29] stated that the FCR dose should be designated to lower the toxicity of the FCR regimen by lowering the dose of both fludarabine and cyclophosphamide while increasing the dose of rituximab to acquire higher efficacy, complete remission, longer survival, and a lower rate of adverse effects. 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*.[30] study in China which reported better treatment response and survival for younger CLL patients than elderly age CLL patients.

Conclusions

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.

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Conflicts of interest

There are no conflicts of interest.

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