Original Article

Cholorambucil versus Cholorambucil Plus Prednisolone as First-Line Therapy of Chronic Lymphocytic Leukemia in West of Iran

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Abstract

Background: Chronic lymphocytic leukemia (CLL) has been the most common type of leukemia in adults worldwide, and then more common in the elderly, markedly more common in patients over the age of 65 years.

Methods: Seventy patients with CLL have referred to Clinic of Hematology-Oncology, Kermanshah, Iran, between Jan 2000 and Jun 2014. We have analyzed age, sex, survival, kind of chemotherapy and type of response in all of the patients with chronic lymphocytic leukemia. Survival curves of complete response patients have compared with partial response, by log-rank test using the Prism 5 GraphPad Software for the five-year period with two years follow up.

Results: The mean age of patients was 61.57±8.88 years that 55.7% were males. Between the 70 patients, 40 patients (57.1%) have started treatment with chlorambucil and 30 patients (42.9%) with chlorambucil plus prednisolone. Among the forty patients that have treated with chlorambucil, overall response rate was 95% that 9 patients (22.5%) had complete response**.** Among the 30 patients that have treated with chlorambucil plus prednisolone, overall response rate was 96%, that 9 patients (30%) had complete response after six months of treatment. The mean of five-year overall survival for treated patients with chlorambucil and chlorambucil plus prednisolone in the first-line of therapy was 38.5 and 40.5 months, respectively.

Conclusion: Combination of prednisolon to chlorambucil has increased survival rate in the patients more than mono-therapy with chlorambucil and also the complete response rate to chlorambucil in West of Iran was better than other areas of world.

Keywords: Chlorambucil; Chronic lymphocytic leukemia; Complete Response; Prednisolone

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Introduction

CLL has known as a disease of mature B lymphocytes, and has been more common in the elderly and markedly more common in patients over the age of 65 years, with an incidence of 22–30 per 100,000 in Western countries [1].

The selection of therapy in patients with CLL should be individualized. The efficacy and toxicity of the treatment regimen, the mechanism of drug elimination, and the patient's underlying organ function had important considerations [2]. Although the overall 5-year survival for patients diagnosed with CLL would be approximately 80%, and the prognosis for patients with advanced CLL was poor [3].

Chlorambucil (marketed as Leukeran) has known as a chemotherapy drug that has been mainly used in the treatment of chronic lymphocytic leukemia. It would be a nitrogen mustard alkylating agent and could be given orally [4]. Chlorambucil's current has well tolerated by most patients, though chlorambucil has been largely replaced by fludarabine as first-line treatment among the younger patients [5]. Prednisolone would be a corticosteroid drug with predominant glucocorticoid and low mineralocorticoid activity, making it useful for the treatment of a wide range of inflammatory

and auto-immune conditions [6]. In this study, we have analyzed chlorambucil and chlorambucil plus prednisolon in CLL patients for the first time in West of Iran as the first-line therapy, to study the effects on Kurdish ethnic.

Materials and Methods

Patients

Seventy patients with CLL have referred to Clinic of Hematology-Oncology, Kermanshah, Iran, between January 2000 and June 2014. This observation was retrospective and most criteria for entering to treatment were B- symptoms, rapid doubling time in WBC and decrease of platelet. The age has not limited the indication of treatment. We have analyzed age, sex and overall survival (OS), kind of chemotherapy and type of response (overall response (OR) rate and complete response (CR) for all of the patients. The CR to different types of drugs has defined as the disappearance of all evidence of disease that required blood count, and then more than 50% reduction, in abnormal lymphadenopathy or hepatosplenomegaly that ultrasonography, CT scan have shown them.

In this study, patients have treated during the six months after diagnosis of CLL with chlorambucil (10 mg/day for 5 days) or chlorambucil (10 mg/day for 5 days) plus prednisolone (50 mg/day for 5 days).

Statistical analysis

The OS has calculated as the time from diagnosis to death (event) or last contact (censored). Survival curves of patients with CR have compared with those with PR by log-rank test using the Prism 5 GraphPad Software for the five-year period with two years of follow up.

Results

The table 1 has shown the variables of seventy CLL patients with the mean age of 61.57±8.88 years (range: 40-84) that 55.7% were males and 44.3% were females. Among the 70 patients, 40 patients (57.1%) have started treatment with chlorambucil and 30 patients (42.9%) have started with chlorambucil plus prednisolone.

Of forty patients that have treated with chlorambucil, six months after treatment, OR rate has 95% that 9 patients (22.5%) had CR (Table 2). Survival rate for complete responders was 75% and survival rate for partial responders was 68% at five years (Figure 2). Also thirty patients have treated

Table 1. The characteristics of the patients with chronic lymphocytic leukemia (n=70).

Variables	n (%)	Mean ±SD
Age		61.57±8.88
Sex		
Male	39 (55.7)	
Female	31 (44.3)	
Start of treatment		
Chlorambucil	40 (57.1)	
Chlorambucil + Prednisolone	30 (42.9)	

Table 2. The response rate of the patients with chronic lymphocytic leukemia to treatment with drug.

Response / Start of treatment	CR n (%)	OR n (%)
Chlorambucil	40 (95)	9 (22.5)
Chlorambucil + Prednisolone	30 (96)	9 (30)

with chlorambucil plus prednisolone that OR rate and CR rate after six months of treatment has located in table 2, and survival rate for complete responders and partial responders has located in Figure 3.There was no significant relationship between survival for complete responders and partial responders ($p>0.05$).

The mean of five-year OS for treated patients with chlorambucil (group 1) in the first-line of therapy was 38.5 months, and survival rate was 69.7% (Figure 1), and for treated patients with chlorambucil plus prednisolone (group 2) in the first-line of therapy, the mean of five-year OS was 40.5 months with survival rate 76%. There was no relationship of significant statistically between survival rates for two groups ($p>0.05$).

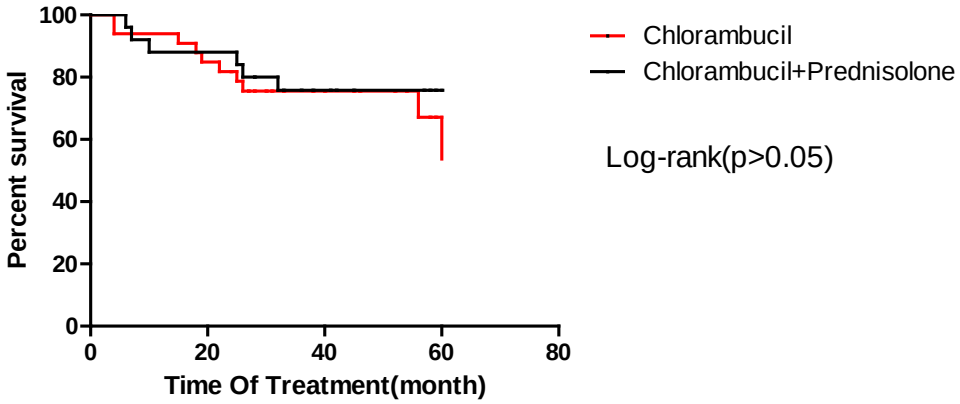

Figure 1. The overall survival for treated patients with chlorambucil, and chlorambucil plus prednisolone.

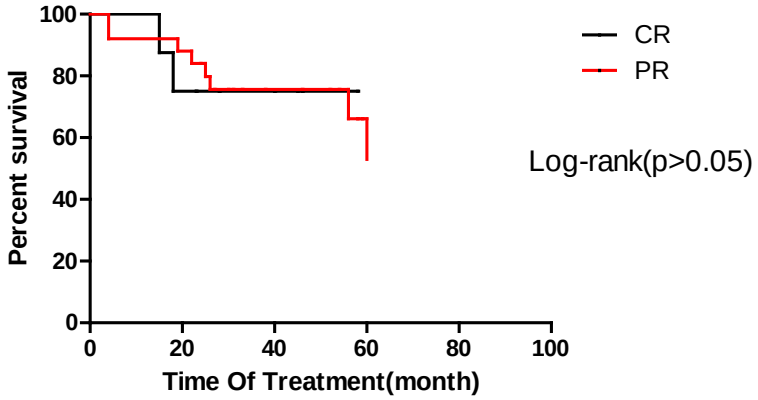

Figure 2. The overall survival from first chlorambucil administration for patients achieved a complete response or partial response.

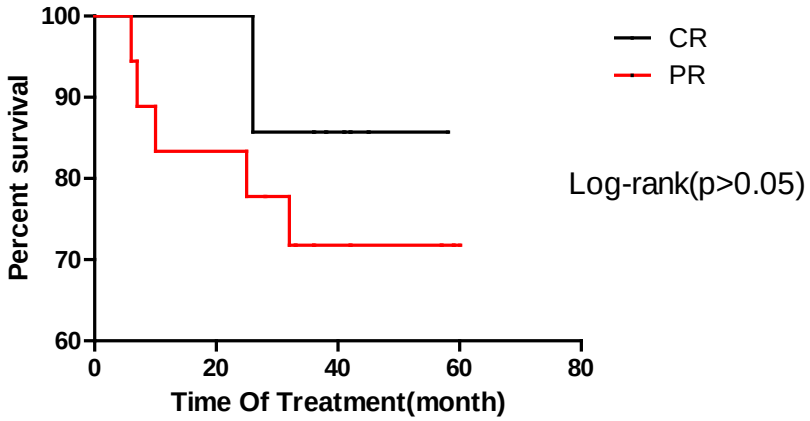

Figure 3. The overall survival from first chlorambucil+prednisolon administration for patients achieved a complete response or partial response.

Table 3. The response rate to treatment with the first-line chemotherapy.

Reference	Treatment (dose)	Patients	OR (%)	CR (%)	PR (%)
5	Chlorambucil (40 mg/m^2 every 28 days)	67	37	4	33
5	Fludarabin (25 mg/m^2/d for 5 days)	170	63	20	43
5	Fludarabin (20 mg /m^2 /d for 5 days) + Chlorambucil (20 mg/m2/d every 28 days)	75	61	20	41
8	Rituximab (375 mg/m^2 and 500 mg/m^2) + Chlorambucil (1mg/Kg)	27	74	26	48
9	Alemtuzumab (30 mg) + Fludarabin (20 mg/m^2/d) + Cyclophosphamide (200 mg/m^2/d) + Rituximab (375 mg/m^2)	60	92	70	22
10	Rituximab + Cyclophosphamide + Vincristine + Prednisolone	20	100	73.6	26.3
11	Lumiliximab (375 mg/m^2 2 or 500 mg/m^2) +Fludarabine (Variable) + Cyclophosphami (Variable) de + Rituximab (Variable)	31	65	52	13
12	Fludarabin + Cyclophosphamide + Rituximab	224	95	72	18
13	Cladribine (12 mg/kg/d) + Prednisone(30 mg/m^2/d)	126	87	47	40
13	Chlorambucil (12 mg/kg/d) + Prednisone (30 mg/m^2/d)	103	57	12	43
14	chlorambucil (0.4 mg/kg orally days 5 and 6) + prednisone (60 mg/m2 orally days 1 to 4)	48	75	27	48
15	Chlorambucil (12 mg orally every days) + prednisone (0.5 mg/kg orally)	41	-	47	-
16	chlorambucil (12 mg/m2 per day for 7 consecutive days) + prednisone (30 mg/m2 per day on days 1to 7)	19	47	16	31
17	Chlorambucil	96	69	3	66
17	Fludarabin	27	89	44	45
18	Fludarabin (25 mg/m(2) intravenously days 1 to 5) + Rituximab(50 mg/m(2) day 1 to 375 mg/m (2) day 1)	102	90	29	61
19	Almatuzumab (30 mg On 3 days) + Rituximab (375 mg/m(2))	30	90	37	53

Discussion

CLL has been the most common type of leukemia in adults worldwide, and the most common type of leukemia in adults worldwide [7]. Chlorambucil, an alkylating agent, was the standard first line treatment for B-CLL/SLL before the development of the purine analogues [8].

There are a lot of studies in word that CLL patients have treated with different kinds of medicines in chemotherapy for the first-line therapy (Table 3). In the number of studies (Table 3) that the patients have treated with mono-therapy or multiple-drug therapy (almost between 3 to 6 months in more of studies), the CR rate has shown the better result for multiple-drug therapy [9-12].

Combination of prednisolone to chlorambucil had a better CR [13-19] compared to chlorambucil alone [5, 17]. Our study has confirmed the results of

these studies but our result was not statistically significant, because regimens of chemotherapy in last 14 years ago for our patients were multiple, caused the results be different. Two studies [5, 17] have reported that CR for the treated patients with chlorambucil were 4% and 3%, respectively, and then in this study, CR was 22.5%. These reports have shown that even in western Iran and Kurdish ethnic, probably chlorambucil alone has given better results compared to other areas [5, 17].

Lamanna et al. [20] has reported sequential therapy with fludarabine --> cyclophosphamide --> rituximab yields improvement in quality of response that the 5-year survival rate was 71% compared with a rate of 48% with our prior fludarabine --> cyclophosphamide regimen. Also Robak et al. [21] has analyzed the efficacy and toxicity of cladribine with cyclophosphamide combination (the CC regimen) in 20 patients with previously untreated B-cell CLL who had 17p13.1 deletion has reported to the Polish Adult Leukemia Group (PALG) registry. The OS probability at 2 years was 52.5%. In this study, for the treated patients with chlorambucil plus prednisone, the mean of five-year OS was 40.5 months and other study [15] has reported that the mean of OS was 48 months. Also in our study, the five-year survival rate for treated patients with chlorambucil alone and chlorambucil plus prednisolon was 69.7% and 76%, respectively. These results have shown that combination of prednisolon to chlorambucil or sequential monotherapy has increased OS and survival rate in the patients.

Conclusion

First of all, Combination of prednisolon to chlorambucil has increased survival rate in the patients more than mono-therapy with chlorambucil. Second, the CR rate to chlorambucil in Western Iran was better than other areas of world and also combination of chlorambucil and prednisolone has shown better CR compared to chlorambucil alone. At last, there was no relationship of significant statistically between survival rates for the treated patients with chlorambucil or chlorambucil plus prednisolone.

Acknowledgement

The authors don't have any acknowledgement.

Conflicts of Interest

The authors have declared that no competing interests exist.

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