Original article

Efficacy of combination of rituximab therapy with chlorambucil plus prednisolone (R-LP) Protocol as treatment line in chronic lymphocytic leukemia patients

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ABSTRACT

Background: Chronic lymphocytic leukemia (CLL) remains an incurable disease with variable course. It is typically responsive to several courses of chemotherapy.

Objectives: Evaluation of efficacy of combination of rituximab with chlorambucil plus prednisolone (R-LP) as first line of treatment of CLL patients whom are not fit for treatment with fludarabine combination therapy.

Patients & Method: Over 17 months duration, thirty patients with CLL were included in this a cohort prospective study. All of them were received 8 cycles combinations of rituximab (day 1) plus chlorambucil plus predinsolon (day1 to day 5). It had been used for those couldn't receive or those having intolerance to fludarabin based therapy. At end of courses , re-assessment had performed & included clinical examination ,blood count in addition to BM examination for evaluation of response in term of overall response rate(ORR) ,duration of response(DOR), and treatment free interval(TFI).

Results: Overall response rate (ORR) reported in 86.67% of patients. Both anemia &bone marrow lymphocyte percentage has significant relation to the treatment response (p=0.051, p=0.036 respectively) as well as positive direct antiglobulin test(DAT) & diffuse BM infiltration (p=0.033,p=0.04 respectively). Mean duration of response (DOR) is 9.23±0.50 months while mean treatment free interval (TFI) is 11.74±0.64 months. Bone marrow lymphocyte proportion is consistently predictive factor in long term remission durability in negative correlation(r = – 0.47, p= 0.04).

Conclusion: Rituximab plus chlorambucil and predinsolon (R-LP) combination therapy might be as good alternative regimen with equivalent response for CLL patients whom are nonsuitable for treatment with fludarabine combination therapy

Key words: chronic lymphocytic leukemia, rituximab, chlorambucil, treatment guidelines.

Introduction:

Indolent B cell lymphoid malignancies including Chronic lymphocytic leukemia (CLL) have many common characteristics like slow growth, a high initial response rate and a variable disease course besides the common cell of origin (mature B cell) [1,2] .

The Rai and the Binet staging system [3,4] are simple yet accurate predictors of survival and are widely used by clinicians and researchers.

The natural history of CLL is extremely variable and survival from initial diagnosis ranges from 2 to 20 years. The watchful waiting strategy is acceptable in most indolent B cell lymphoid malignancies including CLL .[2] ,however; it remains an incurable disease with an extremely variable course. [5]. As a result, therapy must be flexible and individualized for different patient groups [6]

Advances in the treatment of chronic lymphocytic leukemia (CLL) have improved initial overall response rates (ORR), complete response (CR) rates and progression free survival (PFS). [6]

Rituximab is a chimeric mouse anti-human CD20 monoclonal antibody. It is included in the treatment of chronic lymphocytic leukemia (CLL), low-grade or follicular lymphoma, and diffuse large B-cell lymphoma [7]

Combination of rituximab with fludarabine plus cyclophosphamide significantly improved ORR, CR and PFS both in untreated patients with CLL and in those with relapsed or refractory CLL, according to the results of two randomized, open-label, multicenter trials. [7] This improvement is directly resulted from an improved ability to eliminate minimal residual disease (MRD) [6,8]

For many years chlorambucil (LEUKRAN®) has been the standard treatment for CLL for 40 years, but it has not changed the natural history of the disease. [9]. It yields a small proportion of complete responses (5 – 10%) and improves symptoms, but the survival is only slightly, if at all, affected.

Because of this, chlorambucil is usually given to patients not able to tolerate more effective therapies. It should be noted that the doses of chlorambucil have varied widely in different studies and there is a clear indication of a dose – response curve. [10] Chlorambucil is still used as the treatment line in many current trials. Because of its relative safety it is still recommended for patients over the age of 70 years or those with comorbidities [6,9] .

The aim of this study is to evaluate the efficacy of combination of rituximab with chlorambucil plus predinsolon (R-LP) as first line of treatment of CLL patients whom are not fit for other standard first line therapy containing purine analogous.

Patients & Method

It is a cohort prospective study performed at hematology unit, Emammain kadhumain medical city throughout the period from Dec 2011 to May 2013 over 17 months duration.

It included 30 patients diagnosed to have CLL. The diagnosis based on clinical features & the combination of lymphocyte morphology on peripheral blood film as, there is >5 x 10^9/l of circulating mature looking lymphocyte cells persisting for >3 months with either characteristically more than 30% of the nucleated cells in the bone marrow aspirate are mature lymphoid cells [8] in addition to characteristic immunophenotyping markers that confirmed via either immune-histochemistry on bone marrow biopsy or flowcytometry on peripheral blood whenever available (which is defined according to the recommended scoring system allocates one point each for the expression of weak surface membrane immunoglobulins, CD5, CD23, and absent or low expression of CD 79b and FMC7) [11]

A marrow biopsy and aspirate were helpful in evaluation the factors contributing to cytopenias (anemia, thrombocytopenia) that may or may not be directly related to leukemia-cell infiltration of the marrow as well as for the type of marrow infiltration (diffuse vs. non diffuse) which reflects the tumor burden and provides some prognostic information.[8]

The following conditions had been excluded hairy cell leukemia, or leukemic manifestations of mantle cell lymphoma, marginal zone lymphoma, splenic marginal zone, lymphoma with circulating villous lymphocytes, or follicular lymphoma.

Patients data were reported and included age, genders, clinical manifestation, hemoglobin (Hb), white blood cells (WBC), lymphocyte proportion, and platelet count as well as BM aspirate lymphocyte percentage and pattern of distribution at biopsy (diffuse vs. non diffuse). Direct Coombs test (direct antiglobulin test-DAT-) had requested for each.

This study had been approved by local ethical committee for medical researchers at college of medicine Al-Nahrain University, and all patients were informed about therapeutic course &written consent had taken.

All patient were received rituximab (375mg/m2 at first cycle & 500mg/m2 at

subsequent cycles for day 1 only) every 28 day as intravenous infusion over 4-6 hours preceded by premedication (8) in addition to simultaneous use of combination chlorambucil (10 mg/m^2- per oral) plus prednisolone (60 mg/m^2- per oral) from day1 to day 5 as outpatient treatment [12] for 8 cycles.

This course was advised for all patients who couldn't commit to stay inside hospital to receive the classical approved course (due to personal or extraordinary circumstances) or those having intolerance to fludarabine based therapy, like positive DAT or allergy.

During the cycles of chemotherapy, all patients were monitored for any complication of treatments & managed accordingly.

At end of courses, re-assessment had performed and included clinical examination, blood count in addition to re-BM examination for evaluation of response in term of overall response rate (ORR), duration of response (DOR), and treatment free interval (TFI). The definitions of response used in the UK for CLL3 and CLL4 trials were broadly similar to the National Cancer Institute (NCI) 1996 guidelines. These definitions have been updated and clarified in the 2008 IWCLL guidelines [8].

CR requires normalization of blood counts and the bone marrow, whereas a PR requires the regression of at least 50% of organomegaly and lymphocyte counts. A bone marrow aspirate & biopsy are required to define the category of nodular PR by the presence of discrete or moderately large nodules of residual CLL [8]

Follow up monitoring every 2 months had advised & registered for all patient during the time of observation post chemotherapy

Those with failure of treatment had been shifted to another line of treatment.

SPSS version 14 program had been used for statistical analysis &included student t test , Fisher Exact test , Mann Whitney U test and correlation analysis considering $P< 0.05$ as significant.

Results

Demographic characteristics at initial presentation

The total number of patients was thirty. Nineteen (19/30) of them were female (Male: Female = 1:1.73). The mean age is 62.03±1.73 years (mean ±SE). Its range between 45-76 years. Male patients reported higher mean age which is 64.4±2.1years.

The most common initial compliant was listed to be abdominal pain & heaviness (26.67%) as shown in frequency of clinical presentation description (table I).

Those eight patients (26.67%) presented with abdominal pain proved to have

massive splenomegaly despite presence of other 11(36.67%) patients who discovered to have mild to moderate clinically palpable splenomegaly. A radiological enlarged splenomegaly found in 6 (20.0%), while only 5 (16.67) patients found to have not enlarged spleen.

Investigations of the studied patients demonstrated that white blood cells (WBC) count varied between 19.8x 10^9/l - 230.0x10^9/l with mean of 78.42x10^9/l±11.38x10^9/l (the mean absolute lymphocyte count was72.0x10^9/l± 2.2x10^9/l with range between 60.0x109/l -115.0x10^9/l)

Hemoglobin (Hb) mean level was 102g/l±4.1g/l in range between 60-142 g/l while platelet count mean was 141.93x10^9/l ±8.53x10^9/l (65.0x10^9/l - 224.0x10^9/l)

At bone marrow (BM) aspirate, the mean lymphocyte percentage estimated as 64.13%±2.83% while BM biopsy formed mostly diffuse pattern infiltration in 53.3%(16/30) of studied group.

Direct Coombs (DAT) test was screened for all patients but only five showed positive results (16.67%) who were having severe anemia.

Treatment outcome at end of 8 cycles of R-LP courses

All patients had completed their 8 cycles of chemotherapy every 28 days. No serious adverse effects were demonstrated throughout follow up period. Response was assessed depending on clinical examination, laboratory evaluation and sonographic assessment before each cycle while BM study performed at the end of 8 cycles.

Overall response rate (ORR) reported in 86.67% of patients& included complete response in (CR) 50 %(15/30) with partial response (PR) in 36.67% (11/30). Four patients failed to show any primary response that necessitate changing to another protocol.

Concerning their clinical parameters, the age of patients showed no relationship to treatment outcome (p= 0.94) &similarly their gender (p=1.00) as well as the presenting symptoms whether accidentally or not (p=0.39) or the presence of clinically palpable splenomegaly (p=0.45).

Association between different laboratory parameters &treatment outcome revealed that both anemia &bone marrow lymphocyte percentage has significant relation to the outcome (p=0.051, p=0.036 respectively). Those with positive DAT showed worse outcome than their counterparts in statistical significant (p=0.033) as in (table II) while bone marrow diffuse pattern infiltration showed lower response rate to this regimen as most of them got either PR or Failure(68.75%)(11/16) (p=0.04).

Outcome at end of follow up period

Assessment of the long term outcome in terms of survival rate at the end 17 months of follow up in relation to their initial presentation & laboratory parameters demonstrates that both WBC, hemoglobin &positive DAT are associated significantly with long term outcome (p=0.05,p=0.03,p=0.04 respectively) in contrast to other parameters like platelet count or bone marrow lymphocyte percentage or even absolute lymphocyte number. Although the bone marrow pattern persists to be worse marker for long term outcome as 6/16(37.5%) reported death (p=0.051) during follow up (due to different reasons) (table III, table IV)

All other clinical factors don't showed any relationship with long term-outcome apart from age (p=0.03) unlike the gender (p=0.4), the clinical presentation (p=0.3) or the presence of massive splenomegaly (p=1.00)

In terms of correlation, it found that the bone marrow lymphocyte proportion is consistently predictive factor in long term remission durability in negative correlation {the higher the proportion ,the lower remission duration persistence & the earlier chance of relapse}(r = – 0.47, p= 0.04) unlike the rest of parameters (table V)

Discussion

Chronic lymphocytic leukemia (CLL), the most common form of adult leukemia [13,14]. During the last decade, the treatment approach to CLL has dramatically changed from palliative to potentially curative. The goal of treatment has shifted from controlling leukocytosis and disease-related symptoms to achieving eradication of minimal residual disease (MRD) [15]

In this study, the disease reported at mean age of 62.03±1.73 years which is slightly lower than what is published as the median age at diagnosis is between 65 and 70 years [11,13,16] or just similar to Stefano Molica report [17], while the females shown to be predominant affected gender here & this is unlike the reported gender ratio by others who identified that CLL more likely to affect male patients in average ratio of 2 [11,13],this variation may be due to different populations ratio.

Most of studied patient were complained of abdominal heaviness while asymptomatic patient presented second in order unlike Rozman et al report that define that 70% of CLL patients were asymptomatic at time of diagnosis [13]and this may be understood due to sample size as well as inclusion criteria in this study. Positive Direct anti globulin test(DAT) is similar to other reports (16.6% vs. 7.7%-35%) [13]

Therapeutic approaches to CLL should take into account patient classification, when to treat, and the potential role of new drugs. In this study ,the age of patients showed no relationship to treatment outcome(p=0.94) in contrast to the presence of anemia &bone marrow lymphocyte percentage with bone marrow diffuse pattern infiltration that indicate advanced disease stage (p=0.051,p= 0.036, p=0.04 respectively)in agreement of Jaksic et al postulation that tumor mass has a role in diseases outcome [18] and similarly the significance of positive DAT demonstrated worse outcome in statistical point of view (p=0.033) with lower response rate to this regimen later on .

The bone marrow in CLL has traditionally been considered as important prognostic marker [17,19], especially if it is diffusely infiltrated by mature-appearing lymphocytes. The pattern of bone marrow infiltration separates CLL patients into two different prognostic groups [19] Patients with diffuse infiltration have a median survival ranging between 2 and 4 years, while this value is between 8 and 10 years for those with a nondiffuse pattern.

Clinically, The age of patients showed no relationship to treatment outcome (p=0.94) &similarly their gender (p=1.00)as well as the presenting symptoms whether accidentally or not (p=0.39) or the presence of clinically palpable splenomeglay (p=0.45) unlike Lee JS et al who report that advanced age & presence of organomegaly are reliable markers of early prognosis [20]

Chlorambucil, an aromatic derivate of nitrogen mustard, is the old most commonly used drug in CLL, but complete remissions are rarely reported .The combination of chlorambucil and prednisone does not appear to be superior to chlorambucil alone [21], however; it remains widely used in the UK for patients considered unfit for intensive therapy on fludarabine combination regimens but with no international consensus as to the optimal dose or duration of chlorambucil therapy [11] . Therefore David Oscier had encouraged a recommendation for the combination of ant CD 20 antibodies into chlorambucil or benadmustine based regimen in these conditions.[11].

Chlorambucil plus prednisolone, remains the best treatment for patients over 60, because of low side effects, oral administration and relatively acceptable response rates [22], but the responses were heterogeneous.

While it is well known that corticosteroids possess lymphocytolytic activity, prednisone by itself has a limited antileukemic effect in CLL. Nevertheless, it is useful when dealing with autoimmune hematological complications. The limits of corticosteroid treatment in B-CLL are related to the metabolic and/or cardiovascular complications that sometimes appear in long term therapy, especially in the elderly. [23]

CLL is typically responsive to several courses of chemotherapy, although the depth of response tends to decrease with each subsequent line of therapy [24] Response rate in fludarabine based therapy 81% to 100% (25% to 37% CRs) in untreated patients according to O'Brien S. et al (25) while in R-LP regimen used in this study, it showed that (ORR) overall response rate is 86.67% (CR :50%,PR: 36.67%).

A group of leading hematologists have suggested that the toxicity profile of fludarabine (particularly immunosuppression due to long-term T-cell toxicity) makes it unsuitable for around 50% of patients (generally those aged older than 65 years with comorbidities and poor performance status). These patients are treated with chlorambucil, which is generally well tolerated but has relatively poor efficacy compared with fludarabine combination chemotherapy regimens in terms of the depth of remission (22). Chlorambucil therefore tends to be used when clinicians decide to take a palliative approach. (24) (12)

Therefore; FCR(fludarabin-cyclophosphamide- rituximab) is recommended as initial therapy for previously untreated patients (11) (14) but in case of being unsuitable, chlorambucil was the preferred first-line treatment option for patients with CLL who would be considered unsuitable for fludarabine combination chemotherapy regimens (24) and the R-LP might be as good alternative regimen with equivalent ORR although There are currently no definitive criteria for determining which patients would be unsuitable for treatment with fludarabine combination therapy [24]

Conclusion

Rituximab plus chlorambucil and predinsolon (R-LP) combination therapy might be as good alternative regimen with equivalent response for CLL patients whom are nonsuitable for treatment with fludarabine combination therapy

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Potential Conflicts of Interests: author declare no such conflict

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Table I: Frequency of Clinical Presentation

Clinical Presentation	No.	%
Upper abdominal pain &heaviness	8	26.67
Accidental (asymptomatic)	7	23.33
Lymph nodes swelling	5	16.67
Constitutional Symptoms	5	16.67
Anemia	3	10.00
Any Combination	2	6.67
Total	30	100.00

Table II:

Relationship between initial laboratory parameters with treatment outcome at end of 8 cycles of R-LP

Parameter†		CR (n = 15)	PR (n = 11)	Failure (n = 4)	P-value
		Mean±SE	Mean±SE	Mean±SE	
WBC(x 10^9/l)		89.74 ±14.86	88.40±22.09	93.5±29.15	0.757
Hemoglobin(g/l)*		103.4±5.5	98.73±7.3	72.75±4.7	**0.051***
Platelet (x 10^9/l)		117.62±52.58	104.27±57.49	112.50±33.56	0.521
Bone Marrow lymphocyte %*		59.80±3.30	69.30±5.50	91.00±7.65	**0.036***
Absolute Lymphocyte count (x 10^9/l)		72.40±2.98	76.36±4.05	63.75±2.39	0.194
DAT*	Negative	14(46.67%)	11(36.67%)		**0.033***
	Positive	1(3.33%)	4(13.33%)		

†Fisher Exact test * statistical significance

Table III: Final Outcome Summary at end of follow up period

Response duration range (mean ±SE)			
	Duration of Response-DOR (months)	4.00-15.00	(9.23±0.50)
	Treatment free interval-TFI (months)	6.00-18.00	(11.74±0.64)
Patients outcome frequency (percentage)	**Survival**	21/30	(70.00%)
	Death	9/30	(30.00%)
	Total	30/30	(100.00%)

Table IV:

Relationship between final outcomes with their initial presentation in term of survival

Parameter	Out come	N	Mean±SE	P-value*
WBC(x 10^9/l)*	Survival	21	77.53±14.42	**0.05***
	Death	9	105.33± 18.30	
Hemoglobin (g/l)*	Survival	21	112.29± 4.15	**0.03***
	Death	9	94.11±7.3	
Platelet (x 10^9/l)	Survival	21	136.86±52.5	**0.3**
	Death	9	104.40±18.08	
Bone Marrow lymphocyte (%)	Survival	21	73.72±3.59	**0.8**
	Death	9	65.00±4.61	
Absolute peripheral Lymphocyte count (x 10^9/l)	Survival	21	68.38±2.78	**0.6**
	Death	9	87.11±3.61	
Positive DAT**(frequency-percentage)	Survival	4/30	(13.33%)	**0. 04****
	Death	1/30	(3.33%)	

*Mann Whitney U test **Fisher Exact test

Table V:

Correlation between initial presentation and remission durability & treatment free interval

Parameter	Correlation parameter	Age	WBC count	Hemoglobin level	Platelet count	Bone Marrow lymphocyte percentage	Absolute peripheral Lymphocyte
DOR	R	-0.081	0.127	0.193	0.196	**-0.472***	0.297
	P	0.672	0.503	0.308	0.300	**0.043***	0.111
TFI	R	-0.152	0.022	0.169	0.170	-0.260	0.023
	P	0.448	0.912	0.400	0.397	0.190	0.909

DOR: duration of response

TFI: treatment free interval