Five years of experience with rituximab plus high-dose dexamethasone for relapsed/refractory chronic lymphocytic leukemia

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Abstract

Introduction: High-dose methylprednisolone (HDMP) in combination with rituximab is active in the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL), but serious infections are frequent. Recently published data suggested that high-dose dexamethasone might be equally effective as HDMP despite a lower cumulative dose.

Material and methods: We performed retrospective analysis of 60 patients with relapsed/refractory CLL (median age: 66 years; range: 37–86) treated with rituximab plus dexamethasone (R-dex) at a single tertiary center between September 2008 and October 2012. The schedule of R-dex consisted of rituximab 500 mg/m^2 *i.v.* day 1 (375 mg/m^2 in cycle 1) and dexamethasone 40 mg orally on days 1-4 and 10-13 repeated every 3 weeks for a maximum of 8 cycles. Unfavorable prognostic features were frequent (Rai stages III/IV in 67%, unmutated IgVH 82%, del 11q 43%, TP53 mutation/deletion 23%, bulky lymphadenopathy 58% of patients).

Results: Overall response (OR)/complete remission (CR) was achieved in 75/3%. At the median follow-up of 21 months, median progression-free survival (PFS) was 8 months, median time to next treatment 12.9 months and median overall survival 25.5 months. Refractoriness to fludarabine (p = 0.04) and age ≥ 65 years (p = 0.03) were significant predictors of shorter PFS. R-dex was successfully used for debulking before allogenic stem cell transplantation in 7 patients (12%). Serious (CTCAE grade III/IV) infections occurred in 27% of patients; 20% of patients developed steroid diabetes requiring temporary short-acting insulin.

Conclusions: Our results show that R-dex is an active and well-tolerated regimen for patients with relapsed/refractory CLL; however, major infections remain frequent despite combined antimicrobial prophylaxis.

Key words: chronic lymphocytic leukemia, rituximab, dexamethasone, refractory disease, chemoimmunotherapy.

Introduction

Over the past decade there have been major advances in the treatment of chronic lymphocytic leukemia (CLL). The treatment has shifted from a palliative approach characterized by the administration of chlorambucil to aggressive chemoimmunotherapy combining purine nucleoside analogs with the anti-CD20 monoclonal antibody rituximab. Currently the combi-

nation of fludarabine, cyclophosphamide, and rituximab (FCR) is accepted as the gold standard in treatment of younger and physically fit CLL patients [1, 2]. However, the treatment of relapsed/refractory CLL remains highly challenging [3, 4]. High-dose corticosteroids represent a promising option for these patients [5]. High-dose methylprednisolone (HDMP, 1 g/m^2 for 5 days repeated every 4 weeks) has been used in monotherapy [6, 7], in combination with rituximab [8–10] or alemtuzumab, with significant activity [11, 12]. In addition, high-dose corticosteroids demonstrated efficacy in high-risk CLL including patients with tumor protein p53 (TP53) gene mutation and/or deletion [7, 13]. Nevertheless, the treatment is frequently associated with life-threatening infections [14]. The combination of high-dose dexamethasone (40 mg on days 1-4 repeated every 28 days) with rituximab was studied in a small pilot study with resulting similar activity to R-HDMP [15]. The cumulative dose of dexamethasone (320 mg per cycle) is 6 times lower than the dose of methylprednisolone in R-HDMP with regard to relative glucocorticoid activity. It has been demonstrated that the anti-CD20 antibody rituximab and dexamethasone have synergistic antiproliferative and proapoptotic effects *in vitro* [16].

Table I. Baseline characteristics of the study patients

Parameter	*N*	%
Total number of patients	60	
Males	44	73
Median age (range) [years]	66 (37–86)	
Rai modified risk:		
Intermediate	20	33
High	40	67
Bulky lymphadenopathy (≥ 5 cm)	35	58
IgVH genes:		
Mutated	8	18
Unmutated	36	82
FISH:		
Negative	5	11
del 13q sole abnormality	7	16
Trisomy 12	4	9
del 11q	20	43
del 17p	11	23
Median number of previous therapies (range)	2 (1–7)	
Previous treatment with fludarabine	51	85
Previous treatment with alemtuzumab	6	10
Fludarabine-refractory	30	50
Bulky fludarabine-refractory	20	33

IgVH status was assessed in 44 (73%) patients and FISH in 47 (78%) patients; FISH – fluorescent in situ hybridization, IgVH – immunoglobulin heavy chain variable region.

The aim of this study was to perform a retrospective analysis of the efficacy and toxicity of rituximab plus dexamethasone (R-dex) combination in patients with relapsed/refractory CLL.

Material and methods

A total of 60 patients with relapsed/refractory CLL treated at a single tertiary center between September 2008 and October 2012 were included in this retrospective analysis. The schedule of R-dex consisted of rituximab 500 mg/m^2 *i.v.* day 1 (375 mg/m^2 in cycle 1) and dexamethasone 40 mg orally on days 1–4 and 10–13. Treatment was repeated every 3 weeks for a maximum of 8 cycles. Twenty-five patients were included in the analysis published previously [17].

Dexamethasone on days 10-13 was omitted in patients who would require hospitalization for steroid-induced diabetes. Antimicrobial prophylaxis with sulfamethoxazole-trimethoprim, aciclovir or equivalents and fluconazole was used in all patients. Granulocyte colony-stimulating factor was used in the case of grade IV neutropenia.

Assessment of routine prognostic factors (cytogenetic analysis and determination of IgVH mutation status) was performed according to standard practice. The study was conducted in accordance with the Helsinki declaration and all participants signed a written informed consent to treatment form. Treatment response was assessed using standard International Workshop on CLL criteria [18] on an intention-to-treat basis.

Statistical analysis

Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. MedCalc software (MedCalc, Mariakerke, Belgium) was used for statistical analysis. Differences in proportions were assessed by Fisher's exact test. Survival curves were constructed using the Kaplan-Meier method; differences in survival were compared by the log-rank test. Independent predictors of time-to-event were assessed by Cox regression analysis. Patients who received consolidation treatment (e.g. allogenic stem cell transplantation) were censored at the time of consolidation treatment start. *P*-values were considered significant if ≤ 0.05.

Results

Patients displayed highly unfavorable prognostic factors (high proportion of advanced Rai stages,

Table II. Treatment responses

Variable	*N*	%
Overall response	60	75
Complete response	2	3
Partial response	43	73
Stable disease	5	8
Progressive disease	2	3
Not evaluable	8	13

unmutated IgVH, del 11q, bulky disease, fludarabine-refractoriness – see Table I). The median number of administered R-dex cycles was 6 (range: 1–8). Overall response/complete remission (OR/CR) was achieved in 75/3% (Table II). The overall response rate (ORR) for bulky fludarabine-refractory patients (n = 20) was 65% with median progression-free survival (PFS) 6.4 months, time to next treatment (TTNT) 7.5 months and overall survival (OS) 24.7 months. There were no predictors of inferior treatment response (Table III). Treatment response was not evaluable in 8 patients (early discontinuation of treatment n = 4 or early death n = 4). The R-dex regimen was successfully used for debulking before nonmyeloablative allogenic stem cell transplantation in 7 (12%) patients. At the median follow-up of 21 months, the median PFS was 8 months (Figure 1), median time to next treatment was 12.9 months (Figure 2) and median OS was 25.5 months (Figure 3).

Significant predictors of short PFS in univariate analysis were refractoriness to fludarabine (median PFS 14.3 months in fludarabine-sensitive patients vs. 6.8 months in fludarabine-refractory patients, p = 0.04), age ≥ 65 years (median PFS 14 months in patients < 65 years vs. 7.4 months in patients ≥ 65 years, p = 0.03), and response to treatment (median PFS 9.9 months in patients with PR/CR vs. 3.3 months in patients with stable or progressive disease, p < 0.0001), and there was a trend towards shorter PFS in patients with bulky lymphadenopathy (median PFS 6.9 months in patients with bulky lymphadenopathy vs. 8.9 months in patients without bulky lymphadenopathy, p = 0.08) (Figures 4–7).

Table III. Association between prognostic factors and overall response rate

Prognostic factor	ORR	Fisher's exact test *p*-value
Age ≥ 65 vs. < 65 years	71% vs. 80%	0.55
Del17p and/or TP53 mutation	67% vs. 77%	0.47
Bulky lymphadenopathy	74% vs. 76%	1.00
Fludarabine refractory	67% vs. 83%	0.23
Rai stage III/IV	72% vs. 81%	0.54
Splenomegaly	76% vs. 74%	1.00
IgVH unmutated	82% vs. 63%	0.35
Male gender	75% vs. 75%	1.00
Del11q	68% vs. 79%	0.51
Dexamethasone dose 160 vs. 320 mg	68% vs. 73%	0.53

TP53 – tumor protein p53, IgVH – immunoglobulin heavy chain variable region.

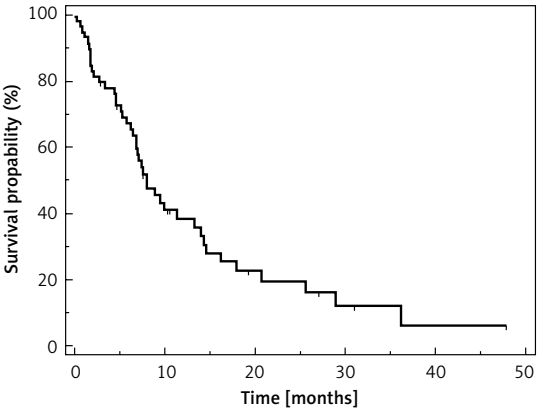

Figure 1. Progression-free survival

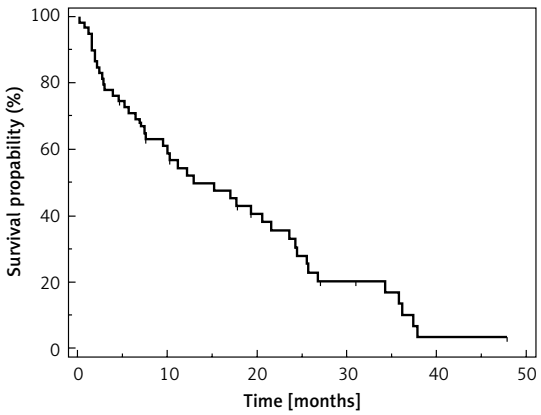

Figure 2. Time to next treatment

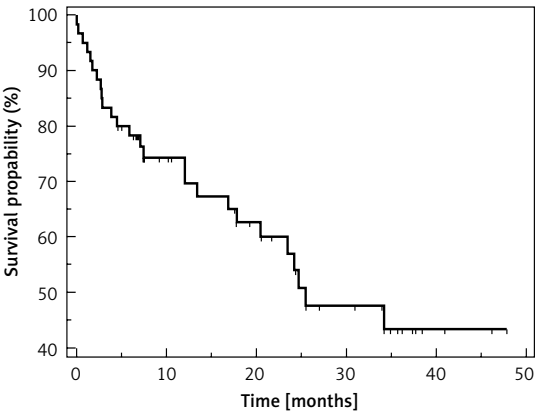

Figure 3. Overall survival

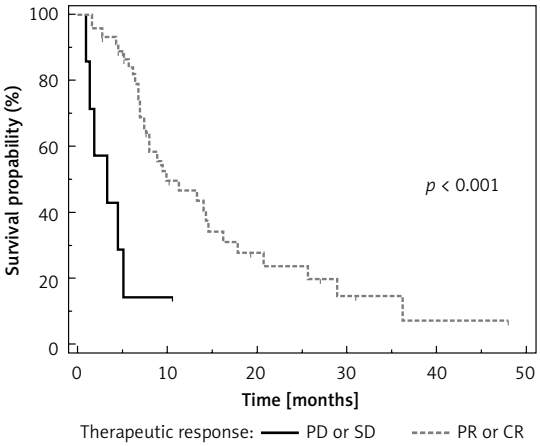

Figure 4. Progression-free survival according to therapeutic response

PD – progressive disease, SD – stable disease, PR – partial response, CR – complete response.

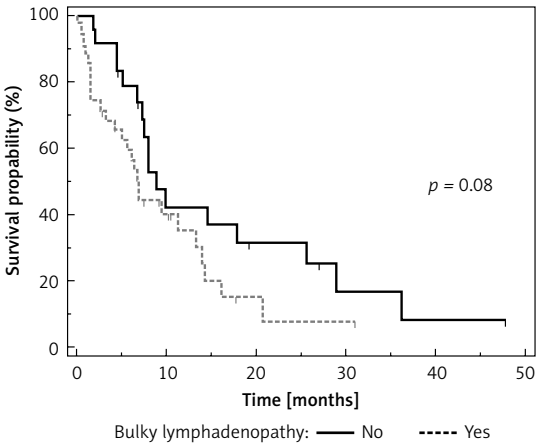

Figure 5. Influence of bulky disease on progression-free survival

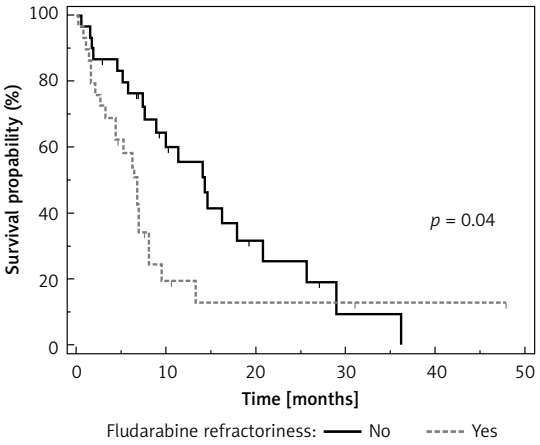

Figure 6. Influence of fludarabine refractoriness on progression-free survival

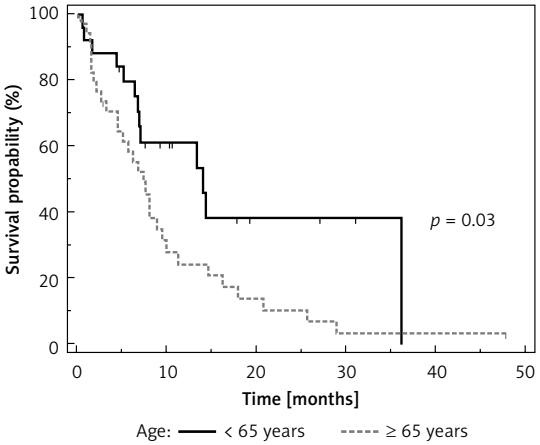

Figure 7. Influence of age on progression-free survival

Absence of therapeutic response and age ≥ 65 years were significant predictors of OS in univariate analysis (Table IV). Notably, higher dexamethasone dose per cycle (320 mg vs. 160 mg) did not result in better treatment outcome. The results of univariate analysis of OS and PFS are summarized in Table IV. In multivariate analysis (included variables: age, bulky lymphadenopathy, fludarabine refractoriness, Rai stage and therapeutic response), age ≥ 65 years and absence of therapeutic response (SD/PD) were identified as independent predictors of shorter PFS (p = 0.002 for both); only age ≥ 65 years was a significant predictor of shorter OS in multivariate analysis (p = 0.006).

Treatment toxicity

The toxic effects of the R-dex regimen were mainly infectious, as expected. Serious infections were observed in 27% of patients. The most frequent were respiratory infections (pneumonia, n = 10 including 2 cases of fatal H1N1 influenza; pulmonary aspergillosis, n = 4). Hematological toxicity was mild: grade III/IV neutropenia was observed in 18% of patients. There were only 3 cases of grade III/IV thrombocytopenia and no cases of severe anemia. Decompensation of diabetes/steroid diabetes occurred in 20% of patients. Treatment-related mortality was 5% (H1N1 influenza, n = 2, invasive pulmonary aspergillosis, n = 1). A total of 31 patients died during the follow-up. Severe toxic effects of the R-dex regimen are listed in Table V.

Discussion

The treatment of relapsed/refractory CLL patients remains a challenging clinical problem [3, 4]. Thornton *et al*. in 1999 first reported the use of high-dose methylprednisolone (HDMP) in this co-

Table IV. Cox proportional hazard regression model for progression-free survival and overall survival

Variable	Median PFS [months]	Univariate analysis	
		Hazard ratio (95% CI)	*P*-value (log-rank)
Age ≥ 65 vs. < 65 years	7.4 vs. 14	2.02 (1.11–3.67)	0.03
Fludarabine refractory vs. sensitive	6.8. vs. 14.3	1.84 (0.99–3.43)	0.04
Bulky lymphadenopathy present vs. absent	6.9 vs. 8.9	1.67 (0.92–3.05)	0.08
Male vs. female gender	7.6 vs. 13.3	1.26 (0.66–2.41)	0.49
TP53 deletion/mutation present vs. absent	8 vs. 8.9	1.25 (0.51–3.06)	0.60
Rai stage III/IV vs. I/II	7.4 vs. 8.9	0.97 (0.51–1.84)	0.92
Splenomegaly present vs. absent	7.6 vs. 9.5	0.93 (0.53–1.77)	0.93
IgVH unmutated vs. mutated	6.8 vs. 8.9	0.87 (0.35–2.18)	0.77
Dexamethasone dose 160 vs. 320 mg	7.6 vs. 9.9	0.68 (0.31–1.49)	0.29
Del11q present vs. absent	6.8 vs. 13.3	0.45 (0.21–0.96)	0.01
Therapeutic response absent vs. present	3.3 vs. 9.9	0.23 (0.05–1.13)	< 0.001
	Median OS [months]	**Univariate analysis**	
		Hazard ratio (95% CI)	***P*-value (log-rank)**
Age ≥ 65 vs. < 65 years	23.5 vs. NR	3.07 (1.41–6.69)	0.02
TP53 deletion/mutation present vs. absent	23.5 vs. 34.2	2.17 (0.67–7.08)	0.09
Bulky lymphadenopathy present vs. absent	24.7 vs. NR	2.02 (0.94–4.36)	0.08
Fludarabine refractory vs. sensitive	23.5 vs. NR	1.97 (0.91–4.28)	0.08
Rai stage III/IV vs. I/II	24.2 vs. NR	1.54 (0.67–3.51)	0.35
Splenomegaly present vs. absent	23.5 vs. 34.2	1.34 (0.62–2.90)	0.46
IgVH unmutated vs. mutated	24.2 vs. NR	1.22 (0.43–3.44)	0.71
Male vs. female gender	24.7 vs. NR	1.11 (0.47–2.58)	0.82
Del11q present vs. absent	23.5 vs. 34.7	1.06 (0.44–2.56)	0.89
Dexamethasone dose 160 vs. 320 mg	25.5 vs. 34.2	0.92 (0.40–2.09)	0.84
Therapeutic response absent vs. present	16.9 vs. NR	0.35 (0.08–1.47)	0.03

PFS – progression-free survival, OS – overall survival, NR – not reached, TP53 – tumor protein p53, CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease.

hort of patients, with promising results [6]. Subsequently the combination of HDMP with rituximab and alemtuzumab was studied by several groups [8–11, 15, 19]. The therapeutic response ranged from 62% to 93% [9, 10, 15, 17, 19]. It is important to note that all of the published results are obtained from small studies with limited numbers of patients; therefore, these publications inevitably suffer from significant selection bias.

The present retrospective study focused on the use of high-dose dexamethasone with rituximab in relapsed/refractory CLL. As already mentioned, 25 patients were included in the previous analysis [17]. This expanded analysis reduced the error of small numbers and heterogeneity of treatment present in the prior analysis. All patients in the present study were treated with the same dosing of rituximab (3-weekly rituximab), as weekly administration of rituximab (3 times per cycle) did not demonstrate better outcomes [17]. Another important aspect is that we excluded patients with autoimmune phenomena (autoimmune hemolytic anemia, immune thrombocytopenia or pure red cell aplasia) as the only indication for CLL treatment. Furthermore, longer follow-up was available to us and so more mature data were obtained. Finally, the statistical analysis was extended compared to the previous publication (e.g., the impact of different prognostic factors on PFS and OS assessed in univariate and multivariate analysis).

Table V. Serious (grade III/IV) toxicity

Adverse event	*N*	%
Infections:	16	27
Pneumonia	10	17
Angioinvasive pulmonary aspergillosis	4	7
Fatal influenza A (H1N1)	2	3
Urosepsis	2	3
Enteritis	1	2
Otitis media	1	2
Hematological toxicity:	11	18
Neutropenia	10	17
Thrombocytopenia	3	5
Steroid diabetes/decompensation	12	20
Treatment-related mortality	6	10

The ORR in our series was 75%, with median PFS of 8 months. These results seem reasonable considering the unfavorable prognostic profile (Rai stages III/IV 67%, bulky lymphadenopathy 58%, unmutated IgVH 82%, del17p 23%) and heavy pretreatment (fludarabine 85%, alemtuzumab 10%). Interestingly, activity of R-dex in bulky fludarabine-refractory CLL was similar to ofatumumab in the registration 406 trial [20] with respect to ORR (R-dex, 75%; ofatumumab, 47%) and PFS (R-dex, median 8 months; ofatumumab, 5.9 months). The results of this extended analysis are similar to the pilot results published previously [17]. Comparison with other studies is difficult because of different patient cohorts (Table VI). For example, patients in two studies [19, 21] were not patients pretreated with alemtuzumab. There was also a marked variable frequency of patients bearing high-risk cytogenetic aberration del17p/mutation p53 between the series, some having very low numbers of patients with del17p [10, 21]. Only 22% of patients in the Mayo Clinic series [8] had bulky lymphadenopathy. Interestingly, efficacy of R-dex in bulky fludarabine refractory patients was comparable to that of ofatumumab in the 406 trial [20]. The present analysis represents the largest series of patients with CLL treated by combination of anti-CD20 monoclonal antibody and high-dose corticosteroids; in addition, patients were treated outside clinical trials in routine practice and there was a high occurrence of unfavorable prognostic factors. Therefore, we believe that these results better reflect real-life conditions of relapsed/refractory CLL treatment. Safety analysis was the second important endpoint of our study. The association of infectious complications with increasing numbers of subsequent treatment lines and fludarabine-refractoriness is a well-known fact. Therefore, the frequency of major infections in previously published studies ranged from 7% to 50% [10, 19, 21]. Grade 3-4 infections occurred in 27% of patients in our series despite combined antimicrobial prophylaxis.

In conclusions, based on our results, R-dex appears to be a good option for treatment of relapsed/refractory CLL outside clinical trials. The regimen also seems to be a suitable choice for debulking before allogenic stem cell transplantation. However, major infections remain relatively frequent despite combined antimicrobial prophylaxis. In addition, durable responses are rare. Thus, further optimization of this therapeutic approach is needed.

Table VI. Publications on high-dose methylprednisolone or high-dose dexamethasone in monotherapy or in combination with rituximab

Author	Year	Regimen	*N*	FR	Del 17p or TP53 mutation	ORR/CR	Median PFS [months]
Thornton *et al.* [6]	1999	HDMP	14	NA	NA	55/0%	8
Bowen *et al.* [8]	2007	HDMP	37	NA	33%	78/22%	12
Dungarwalla *et al.* [10]	2008	R-HDMP	14	NA	7%	93/14%	7
Quinn *et al.* [15]	2008	Dex, R-dex	12	NA	8%	75/8%	14*
Castro *et al.* [21]	2009	R-HDMP	28	NA	4%	93/36%	30
Pileckyté *et al.* [19]	2011	R-HDMP	29	34%	31%	62/0%	12
Smolej *et al.* [17]	2012	R-Dex	54	NA	19%	66%/NA	7
Šimkovič *et al.* (present analysis)	2016	R-Dex	60	50%	23%	75/3%	8

*N – number of patients, PFS – progression-free survival, FR – fludarabine-refractory, TP53 – tumor protein p53, ORR – overall response, CR – complete response, HDMP – high-dose methylprednisolone, R – rituximab, Dex – dexamethasone, NA – not available. *Duration of response.*

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Conflict of interest

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