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ORIGINAL ARTICLE

Rituximab in the therapy of stage III and IV follicular lymphoma: Results of the REFLECT 1 study of the Serbian Lymphoma Group

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Summary

Purpose: *Follicular lymphoma (FL) is an indolent lymphoma that responds well to rituximab+chemotherapy. We evaluated the prognosis and efficacy of immunochemotherapy in patients with previously untreated, advanced FL.*

Methods: *REFLECT 1 is a multicentre, prospective study of 99 patients with previously untreated FL stage III-IV. All patients were treated with rituximab+chemotherapy x 6 cycles, plus 2 cycles of rituximab monotherapy. Clinical assessment was performed at baseline, after completion of the first 6 cycles of therapy and every 3 months from the end of immunochemotherapy to the end of the study period.*

Results: *Eighty-nine out of 99 patients with complete documentation were included. Complete remission (CR) was achieved in 61.6%, partial remission (PR) in 11.6% and progressive disease (PD) in 24.4% of the patients. Time to progression (TTP) and overall survival (OS) after the 1st, 2nd and 3rd year were 89.9, 72.7, 57.8%, and 94.2, 92,6 and 92.6%, respectively. The probability of achieving CR was significantly lower in the high risk group according to Follicular Lymphoma Prognostic Index (FLIPI) score. Expression of CD43 antigen had a significant impact on the probability of 2-year TTP and OS, and ECOG performance status had a significant impact on OS.*

Conclusions: *Treatment with rituximab plus chemotherapy is effective in advanced stages of FL. Significant prognostic factors are FLIPI score for induction therapy outcome, CD43 antigen expression for OS and TTP and ECOG performance status for OS.*

Key words: *advanced follicular lymphoma, induction immunochemotherapy, prognosis*

Introduction

FL is an indolent lymphoproliferative disease that accounts for 20-30% of non-Hodgkin's lymphomas and about 70% of indolent lymphomas [1]. Significant pathogenic disorders in FL include t(4;18)(q32;q21) translocation with an overexpression of anti-apoptotic bcl-2 protein, and disorders in the tumor microenvironment [2,3]. Histological transformation into aggressive, diffuse large B-cell lymphomas occurs in 2-3% of patients annually [4]. The standard initial therapy in ad

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%vanced stages of FL is a combination of rituximab and cytotoxic regimens with or without anthracyclines, with fludarabine, bendamustine and other drugs. Response to the initial immunochemotherapy is relatively good, but with frequent relapses and progressively shortened remission periods without a plateau in the patient survival curve [5]. Of prognostic importance are the patients' features and the parameters of tumor mass size, integrated into the standard FLIPI [6] and GELF score [7], as well as the histological type, changes in the tumor microenvironment, and the assessment of therapeutic effect by PET imaging or by measuring the minimum residual disease [8].

The Serbian Lymphoma Group conducted the REFLECT 1 prospective study in order to assess the effect of rituximab combined with chemotherapy in the initial treatment of stage III and IV FL. This article presents the results of immunochemotherapy and assesses the prognostic values of the standard prognostic parameters in 89 patients with stage III-IV FL.

Methods

The REFLECT 1 prospective, multicentre, nonintervention study of the Serbian Lymphoma Group was conducted from 14 April 2008 to 5 November 2013 and involved 99 patients with stage III and IV FL who were treated with a combination of rituximab and chemotherapy. The data concerning 89 patients with adequate medical documentation was analyzed from 6 clinical centres in Serbia: 21 patients from the Clinical Centre of Vojvodina, Novi Sad, 19 patients from the Oncology Institute of Vojvodina, Sremska Kamenica, 16 patients from the Clinical Centre of Serbia, Belgrade, 15 patients from the Clinical Centre of Kragujevac, 9 patients from the Clinical Centre of Nis, and 9 patients from the Bezanijska Kosa Clinical Hospital Centre, Belgrade. All of the participants gave written informed consent prior to enrollment in the study. The study was approved by the local ethics committees and performed according to the Helsinki declaration. The median patient monitoring time was 23 months, and 6 patients died by the time the study was concluded.

FL was diagnosed by immunohistochemical examination of the material biopsied from lymph nodes: the expression of monoclonal immunoglobulin light chains, CD10+/-, CD19+, CD20+, bcl2+, CD5-, cyclinD1-. The stage of disease was established according to the Ann Arbor criteria [9], and the histological type according to the WHO classification [10,11].

Out of the 99 patients, 89 with complete medical documentation were included in the analysis. The effect of induction therapy was assessed in 86 patients, as one patient was excluded due to an early allergic response to rituximab, one patient died of prostate cancer after the second induction course, and one patient left the treatment on his own initiative.

The patients were treated with a combination of rituximab 375 mg/m^2 and standard chemotherapy (R-CHOP or R-CVP) administered in 6 28-day cycles, plus 2 additional cycles of monotherapy with rituximab. No rituximab maintenance therapy was given. The effect of therapy was assessed at the end of the third and the sixth courses and at the end of the therapy according to the standard criteria [12]. The patients who died during the induction therapy due to progression of disease were included in the assessment of the effect of immunochemotherapy. OS was measured from study entry to patient's death or the conclusion of the study, while TTP was calculated from complete remission to disease relapse or the conclusion of the study.

The prognostic value of the following parameters was assessed: patient sex and age, ECOG performance status, histological type, stage of disease, presence of B symptoms, type of induction therapy, FLIPI [6], bulky disease according to the Groupe d'Etude des Lymphomes de l'Adulte (GELF) criteria [7], Ki-67 expression, and the expression of CD10 and CD43 antigens.

Statistics

The objectives of the prognosis were the probability of inducing CR, 2-year TTP and 2-year OS. All the prognostic parameters were analyzed as categorical variables.

The significance of impact of the prognostic parameters on the probability of CR induction was assessed by Fisher's exact test. The TTP and OS plots were constructed by the Kaplan Meier method, and the significance of impact of the prognostic parameters was evaluated by the log-rank test. A two-sided p value <0.05 was considered as statistically significant.

Results

Patient characteristics and the data on induction therapy are presented in Table 1. The patient median age was 56 years (range 31-80), with a slight predominance of females (56.2%). Bulky disease existed in 31.5% of the patients, and histological type 3 was found in one quarter of them. According to the FLIPI score, 11.2% of the patients were in the low-risk group, and 47.2% were in the high-risk group. More than 75% of the patients were treated with R-CHOP, one patient received R-FCM, and the rest were treated with R-CVP combination.

CR was achieved in 53 patients (61.6%), PR in 10 (11.6%), SD was found in 2 (2.3%) patients, and PD in 21 patients (24.4%). Overall response rate

Table 1. Baseline patient characteristics and type of induction therapy

Characteristics/Parameters	*n*	*%*
Age, years, median (range)	56	(31-80)
Age >60 years	32/89	35.9
Gender, female	50/89	56.2
ECOG >1	13/89	14.6
B-symptoms present	42/89	47.2
Ann Arbor stage IV	49/89	55.1
Bulky disease present (GELF)	28/87	32.2
Histology		
Type 1	28/83	32.5
Type 2	32/83	38.5
Type 3a	21/83	25.3
Type 3b	2/83	3.7
Type 3a+3b	23/83	29.0
FLIPI risk group		
Low	10/89	11.2
Intermediate	37/89	41.6
High	42/89	47.2
Ki67+ >20%	27/62	43.5
CD10+	56/66	84.8
CD43+	10/44	22.7
Induction therapy		
R-CHOP	78/89	87.6
R-CVP	10/89	11.2
R-FCM	1/89	1.2

Table 2. Effects of induction immunochemotherapy in stage III-IV FL

Outcomes	*n*	*%*
Complete remission (CR)	53/86	61.6
Partial remission (PR)	10/86	11.6
Overall response (CR+PR)	63/86	73.2
Stable disease (SD)	2/86	2.3
Progressive disease (PD)	21/86	24.4
Time to progression (TTP)		
TTP at 1 year		89.9
TTP at 2 years		72.7
TTP at 3 years		57.8
Overall survival (OS)		
OS at 1 year		94.2
OS at 2 years		92.6
OS at 3 years		92.6

was 73.3% or 63 patients. The median TTP and OS were not reached, and the projected TTP and OS after the 1st, 2nd and 3rd year were 89.9, 72.7, and 57.8%, and 94.2, 92.6% and 92.6, respectively (Table 2).

The probability of inducing CR was significantly lower in the high risk group, according to the FLIPI score, in comparison with the intermediate- and low-risk groups. The FLIPI score was the only parameter with a significant impact on the outcome of the induction therapy (Table 3). The FLIPI score also had an impact on the probability of 2-year TTP, though at the margin of statistical significance (p=0.064), while it had no significant impact on the duration of OS (Table 4).

Expression of CD43 antigen had a significant impact on the probability of 2-year TTP and OS. The 2-year TTP and OS was 48.6 and 80.3% in CD43+ patients, and 80.3 and 96.9% in CD43- patients (p=0.007) (Table 4). Besides the FLIPI score, the expression of CD10 antigen had a marginal impact on TTP. TTP at 2 years was 100% in CD10-patients, and 65.1% in CD10+ patients (p=0.065) (Table 4).

In addition to the expression of CD43 antigen, ECOG performance status also had a significant impact on OS, while age of the patients older than 65 and the presence of B symptoms had a negative impact of borderline significance (p=0.67). The probability of 2-year OS in patients with ECOG performance status of 0,1 and above 1 was 98.6 and 57.1%, respectively (p=0.01), while 5 of the 6 patients who died by the time of conclusion of the study had a low performance status.

The other analyzed parameters, including histological type of FL, patient sex and type of immunochemotherapy, did not have a significant impact on the probability of inducing remission and the probability of 2-year TTP and OS.

Discussion

The median patient age was 56 years, similar to the average age of patients treated in the academic medical institutions in the USA, and identical with the age of patients with stage III-IV FL in a German study [13]. The age of patients was included in the FLIPI scores as a significant prognostic factor [6,15], but it had a marginal impact on the survival rate of patients and had no significant impact on the probability of inducing remission and prolong TTP, which is likely a consequence of the fact that FLIPI scores concern all the stages of FL, while our study was limited to stages III and IV of disease. The German Low Grade Lymphoma Study Group [14] showed similar results, as of all the parameters included in the FLIPI score in stage III-IV FL only the levels of LDH and haemoglobin significantly impacted the duration of response, while the patient age and the number of affected groups of lymph nodes lacked prognostic significance. Similarly to the above study, bulky disease as defined by the FLIPI

Table 3. Prognosis of induction therapy outcomes

	Complete remission		*p value*
Parameter	*n*	*%*	
Age (years)			
> 60	17/33	51.5	0.2929
≤ 60	36/53	67.9	
Gender			
Male	26/38	68.4	0.1717
Female	40/48	80.8	
ECOG			
0, 1	47/74	63.5	0.573
>1	6/12	50.0	
B symptoms			
Present	23/40	57.5	0.498
Absent	30/46	65.2	
Ann Arbor stage			
III	25/38	65.8	0.824
IV	28/48	58.3	
Bulky disease (GELF)			
Present	14/27	51.8	0.658
Absent	38/58	65.5	
Histology			
Type 1	12/27	44.4	0.169
Type 2	22/32	68.7	
Type 3a+3b	17/23	73.9	
FLIPI risk group			
Low	6/9	66.7	0.009
Intermediate	27/37	66.7	
High	20/40	50.0	
K67+ (%)			
≥ 20	17/25	68.0	0.626
< 20	19/35	54.3	
CD10			
Positive	31/54	57.4	0.262
Negative	8/9	88.9	
CD43			
Positive	5/9	55.6	0.303
Negative	21/32	65.6	
Induction therapy			
R-CHOP	47/76	61.8	0.775
R-CVP + R-FCM	6/10	60.0	

and GELF criteria had no prognostic significance in our patients [6,7].

Women predominated slightly in our FL patient population, which was similar to sex distribution in other studies [13,14,17]. The percentages of CR, 2-year TTP and OS were statistically even for males and females, with the exception that PD was more frequent in males (15.6 vs 6.3%, p<0.05; data not shown). According to the results of Jager et al. [17], the percentage of CR induced by immunochemotherapy was 86% in females and 47% in males (p=0.05), and the females had a longer response and a higher survival rate. Pharmacokinetic analyses have shown that therapeutic concentrations of rituximab in the blood remained longer in females, as well as in patients of both sexes without bone marrow infiltration [17].

ECOG performance status (>1) was found in 14.6% of our patients and it had a significant negative impact on survival, but no influence on the outcome of induction therapy and TTP. The patients with a worse performance status had a significantly shorter survival duration (Table 4). Performance status had a significant prognostic importance in the univariate analysis, but it was not included in the original FLIPI score due to a relatively small number of patients with ECOG>1 and a large difference in the frequency between the European centres (14.5%) and the centres in the USA (2.1%) [6].

The original FLIPI score was constructed based on patients in all stages of FL, with equal distribution in low-risk (36%), intermediate-risk (37%) and high-risk (27%) groups, and it has proven reliable, especially in terms of duration of therapeutic response and patient survival [6]. Our study was limited to patients with stage III and IV FL, therefore the number of parameters included in the score was reduced as dictated by the patient distribution. The largest number of our patients was in the high-risk group (47.2%), and the lowest in the low-risk group (11.2%), which is virtually identical to the distribution of patients in the German study [14]. The FLIPI score in our study presented as the only significant predictor of remission induction, yet with marginal significance on TTP, but it separated well only the high-risk patients from the rest of them. The German study, which involved a large number of FL patients with stage III and IV revealed similar results: the FLIPI score had a significant impact on the length of therapeutic response, but it separated well only the high-risk patients from the other two groups [14].

A total of 78 patients were treated with R-CHOP, and only 11 were administered regimens without anthracyclines. Over 60% CRs and more than 10% PRs were achieved, with a total therapeutic response of 73.2%, which is consistent with the results of the R-CVP and somewhat lower than the results of the R-CHOP regimen in other studies involving all stages of FL [18,19], but very similar to the results of the R-CHOP regimens in stages III and IV of the disease [14]. In our patients, R-CHOP did not prove better than the regimens without anthracyclines, either with regard to CR induction probability, or to duration of TTP and OS. According to an Italian randomized study, which compared the R-CHOP, R-CVP, and R-FM regimens, all

Table 4. Prognosis of time to progression (TTP) and overall survival (OS)

Parameters	*TTP at 2 years* %	*p value*	*OS at 2 years* %	*p value*
Age, years				
>60	69.5	0.737	84.1	0.066
≤60	87.4		97.1	
Gender				
Male	80.8	0.879	81.6	0.2852
Female	82.5		91.7	
ECOG performance status				
0,1	73.7	0.601	98.6	0.01
>1	70.0		57.1	
B symptoms				
Present	67.3	0.667	86.7	0.067
Absent	78.7		97.8	
Ann Arbor stage				
III	72.0	0.807	97.4	0.164
IV	75.3		88.7	
Bulky disease (GELF)				
Present	84.0	0.458	92.4	0.930
Absent	69.6		92.5	
Histology				
Type 1	56.1	0.539	90.3	0.942
Type 2	55.2		93.6	
Type 3a+3b	57.0		91.3	
FLIPI risk group				
Low	68.4		100	0.169
Intermediate	75.1		97.0	
High	43.3	0.064	86.5	
Ki67+ (%)				
≥ 20	80.6	0.409	88.0	0.153
< 20	65.4		97.1	
CD10				
Positive	65.1	0.065	90.7	
Negative	100.0		100	
CD43				
Positive	48.6	0.046	62.2	0.007
Negative	80.3		96.9	
Induction therapy				
R-CHOP	78.7	0.7851	85.1	0.8208
R-CVP + R-FCM	83.3		88.2	

the regimens achieved equal percents of CR (73, 62 and 72%), but TTF after 3 years was significantly longer after the R-CHOP (62%) and R-FM (59%) than after the R-CVP regimen (46%). However, the risk-benefit ratio was significantly higher in the R-CHOP than in the R-FM regimen [20]. According to Japanese authors, R-CHOP is associated with higher CR rate, shorter time to response, longer duration of remission, but higher rate of toxicity than R-CVP, while intensifying the therapy to the R-CHOP 14 regimen does not achieve better effects that the R-CHOP 21 regimen [21]. According to the results of the National Lympho-Care Study in FL stages III and IV, 47% of the patients were treated with R-CHOP, 31% with R-CVP, and 22% with R-Fludarabine, and the R-CVP regimen achieved a significantly lower percentage of remissions, shorter period without progression

and shorter survival [13]. A meta-analysis of the studies comparing results of immunochemotherapy with and without anthracyclines has shown that the percentages of remissions were equal, but the therapeutic response to the anthracycline regimens was better and significantly longer [22]. Similar or somewhat better results, with lower toxicity, are achieved with a combination of rituximab+bendamustine [23]. In our study, there were no differences between the R-CHOP and R-CVP regimens in terms of CR, TTP and OS. However, the number of our patients who were treated with R-CVP is far too small to be able to make sound conclusions about the therapeutic value of R-CHOP in comparison to anthracycline-free regimens.

Literature data on the significance of anthracyclines, i.e. the R-CHOP regimen in the therapy of type 3 FL, and particularly type 3b FL, are contradictory in that they range from data indicating that the R-CHOP increases the percentage of CR, prolongs the TTP and OS and reduces the risk of transformation into aggressive lymphoma [24], to the data showing no difference whatsoever between the R-CHOP and R-CVP regimens [25]. The histological type of FL had no prognostic significance in our study in relation to the probability of inducing remission, and prolong TTP and OS, but the number of patients with type 3b FL who were treated with anthracycline-free therapy was too small to draw any conclusions.

The dilemma whether asymptomatic patients with stage III and IV FL should be treated or only monitored until the appearance of symptoms, especially if they do not have bulky disease, has not been fully resolved. The Italian F2 prospective study has shown that rituximab-based therapy in advanced stages of FL without bulky disease has no advantages over the watch and wait policy [26]. Symptomatic FL was present in about half of the patients included in the study, and the presence of B symptoms had a marginal impact on 2-year survival of patients and no significant impact on the probability of CR induction and the duration of therapeutic response. Of the 6 patients who died by the time of the study conclusion 5 had B symptoms at the time of establishing diagnosis. The number of patients included in our study is relatively small for making valid conclusions, but our results directly indicate a potential advantage of the watch and wait policy in asymptomatic patients in the advanced stages of FL.

Expression of the CD43 antigen was the only parameter with a significant negative impact on TTP and OS in our patients. CD34 is a transmembrane glycoprotein which is expressed in various hematopoietic cells, including B-lymphocytes. The physiological role of CD43 is not fully understood, but it takes part in transducing signals and vital functions of B-lymphocyte precursors, as well as in the differentiation, apoptosis, and migration of T-lymphocytes [27,28]. CD43 is differently expressed in different types of lymphomas, including FL [29]. The prognostic significance of CD43 expression was studied mostly in ocular and diffuse large B-cell lymphomas (DLBCL) [30-32]. CD43 expression significantly lowers the probability of inducing remission and shortens event free survival and OS [31,32]. Interestingly, the prognostic impact of CD43 expression was significant only in patients treated with a combination of rituximab+chemotherapy, but not in patients treated with CHOP only, which points to a possibility that CD43 interferes with the biological effects of rituximab [31]. The research conducted by Mitrovic et al. [32] on the molecular level showed that CD43 expression was more frequent in non-germinal centre B-cell DLBCL and that the prognostic impact may be associated with unfavorable tumor microenvironment. Our results about the prognostic impact of CD43 expression in FL should be examined on a larger number of patients in different stages of disease.

Expression of the CD10 antigen had a borderline statistical significance with regard to the probability of TTP at 2 years: 100% in CD10 negative patients and 65% in CD10 positive patients. The CD10 antigen is expressed in 75% of patients with FL and, together with BCL6 and PU.1, it is associated with germinal centre and has a potential prognostic significance [33,34].

The results of the REFLECT 1 study of the Serbian Lymphoma Group show that immunochemotherapy with rituximab in stage III-IV FL achieves more than 60% CRs and over 10% PRs, with the probability of 3-year survival exceeding 90% and 3-year progression free survival of 57.8%, which is similar to the results of other centres [13,19,20]. The initial immunotherapy with anthracyclines did not show better results than the anthracycline-free regimens. The FLIPI score had a significant impact on the CR induction and a marginal impact on the progression-free time, but only in that it could separate the high-risk group from the other risk groups. The only factor with a significant impact on OS and TTP was the expression of the CD34 antigen, but its prognostic value should be examined on a larger number of patients. ECOG performance status had a significant impact in terms of shortened OS of patients,

while the presence of B-symptoms, patient age and expression of the CD10 antigen had a marginal prognostic significance.

Conflict of interests

The authors declare no conflict of interests.

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