A Success Story: How a Single Targeted-Therapy Molecule Impacted on Treatment and Outcome of Diffuse Large B-Cell Lymphoma

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Abstract. *Diffuse large B-cell lymphoma (DLBCL) is a rather aggressive disease and the natural course of this lymphoma is very dismal. However, first the introduction of anthracycline-containing chemotherapy regimens and then the addition of rituximab were important steps forward. Since no complete real-life analyses have yet been published, we analyzed all patients with DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in the whole region of Tyrol and compared the results to a historical CHOP(-like)-treated cohort. Two hundred and nineteen consecutive patients underwent R-CHOP and 72% achieved a complete remission (CR); 20% suffered a relapse and 31% died. 5-Year progression-free survival (PFS) and overall survival (OS) were 56% and 69%, respectively. We identified several parameters influencing PFS and OS significantly in univariate analysis, but only stage III/IV and hemoglobin <13 g/dl were independent prognosticators for PFS and age >60 years for OS. In comparison to the CHOP(-like)-treated group, the CR rate was similar, while the percentage of relapse was nearly twice in the historical cohort, namely 44%. This translated into a dramatically improved PFS and OS for the R-CHOP group. In conclusion, in a real-life setting R-CHOP results in high percentages of response and long-term remission. Moreover we showed that in the rituximab era, factors other than the single parameters of the international prognostic index significantly influence PFS and OS. Finally, we confirm the independent impact of rituximab on the outcome of an unselected population with DLBCL.*

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Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), accounting for approximately 30% of all new diagnoses (1). It is a rather aggressive disease and the natural course of this type of NHL is very dismal. However, introduction of anthracycline-containing chemotherapy regimens, and cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)(2) in particular, significantly improved the outcome of patients affected by this disease, with the potential of long-term remission and cure. Since the development of this regimen in the early 1970s, several attempts to improve the survival of these patients by aggressive and consequently more toxic regimens failed (6).

In the late 1990s, with the introduction of the chimeric monoclonal antibody against cluster of differentiation 20 (CD20), rituximab, a new era for the treatment of this disease began. Despite the numerous prospective trials demonstrating benefit of rituximab addition to therapy (3, 4, 5), up to now, only a few population-based, retrospective analyses evaluated whether this significant impact of rituximab on survival is also observed in real life (6, 7, 8, 9). These register-based analyses, comparing the outcome

of patients who underwent CHOP without or with rituximab (*i.e.* R-CHOP), retrospectively confirmed the positive effect of this targeted therapy. Nevertheless, the population-based analysis from British Columbia, Canada, included only patients with advanced stage and patients were divided into those of a pre- and post-rituximab era (9). However, in the pre-rituximab era, some patients received the drug and *vice versa*. The second analysis was also performed in Canada (Ontario) and included many more patients which were identified from the New Drug Funding Program of Cancer Care Ontario, while important clinical parameters such the international prognostic index (IPI) and stage of disease were missing. Data from Sweden regarded only very elderly patients (6) and the German registry-based analysis lacked important clinical information (7).

In order to provide a complete real-life analysis of European reality, we analyzed clinical characteristics of all DLBCL cases of our hospital-based registry who were treated in the first line with R-CHOP (10); we aimed to depict clinical and laboratory parameters predicting outcome; and finally compared them to a historical cohort of patients on CHOP (11) regarding clinical characteristics at the time of diagnosis and outcome.

Patients and Methods

Between 1999 and 2012, 215 consecutive patients affected by DLBCL were referred to our Center and underwent R-CHOP therapy (10). Clinical parameters at the time of diagnosis, outcome and survival were compared to those of a historical cohort of 88 patients (11) who underwent CHOP (n=64) or CHOP-like (n=24) (6) chemotherapy without rituximab between 1988 and 2000. The criterion for patient recruitment was the intent-to-treat administration of six cycles of (R-)CHOP. Therefore, patients who required a treatment modification (*e.g.* deletion of vincristine), or those who switched to salvage chemotherapy in case of an insufficient treatment response were included in the present analysis.

Chi-square test was performed to assess the significance of differences between categorical variables. Response was assessed with computed tomography (CT) or positron emission tomography (PET)-CT, applying the international response criteria for malignant lymphoma (12, 13). Overall survival (OS) and progression-free survival (PFS) were plotted as a curve using the Kaplan–Meier method. OS was defined as time from diagnosis until death of any cause; PFS was defined as time from diagnosis until progression of disease or death, whatever occurred first (13). Log-rank test was employed to assess the impact on survival of categorical variables. In order to identify variables with an independent impact on OS and PFS, a Cox multivariate analysis was performed. A *p*-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software v.17.0.1 (SPSS, Chicago, IL, USA). This study was approved by the Ethics Committee of the Innsbruck Medical University (UN3250; 266/4.1). Due to the anonymous data collection, informed consent was not required.

Results

Patients. In the R-CHOP group (n=219), at time of diagnosis the median age was 63 years (range=18-90 years). Most patients presented with stage III/IV disease (56%), and elevated lactate dehydrogenase occurring in 57% (Table I). Other poor prognosticators were the presence of systemic symptoms in 41%, two or more involved extranodal sites in 31% and bone marrow involvement in 11%. A poor prognostic IPI was present in 26% of patients. Patient characteristics in the CHOP/CHOP-like group are also detailed in Table I.

Outcome in DLBCL treated with R-CHOP. Two hundred and nineteen consecutive patients underwent R-CHOP. After a median of six immunochemotherapy cycles (range of 1-10), 72% of patients (Table II) achieved a complete remission (CR), while only a minority of patients had only partial or no treatment response. The percentage of relapses was 20%. During the observation period, 31% of patients died and 34% of them from their disease.

After a median follow-up of 3.5 years (range: 1 month to 12.5 years), the 5-year estimated PFS was 56% (Figure 1) and the 5-year estimated OS was 69% (Figure 1). All clinical parameters assessed at the time of diagnosis in the R-CHOP group were first evaluated for their impact on PFS in univariate analysis (Table III). Of the analyzed parameters, abnormal platelet count, white blood cell count, renal impairment and obesity did not influence PFS (data not shown). Variables significantly influencing PFS were added to the multivariate Cox model. Overall, 103 patients were evaluable for this analysis. Advanced stage III/IV disease, as well as anemia, emerged as independent negative prognosticators for PFS (Table III). The same procedure was performed for OS and of the analyzed parameters, abnormal platelet count, white blood cell count and obesity did not influence OS (data not shown). In the Cox regression analysis (115 patients included), age greater than 60 years was an independent negative prognosticator of OS.

Outcome of DLBCL patients in the pre- and post-rituximab era. In order to evaluate whether the addition of rituximab to CHOP improved the outcome of patients with DLBCL, we carried out a direct comparison to a historical cohort of 88 patients (Table I). In both groups, the percentage of CR was similar (72% for R-CHOP and 70% for CHOP/CHOP-like) (Table II). The median number of chemotherapy cycles was equal in both groups (six cycles). However, the percentage of relapses varied in a statistically significant manner between groups (p=0.001), being 20% in the R-CHOP group and 44% in the other. This translated into a clearly higher death rate in the CHOP group of 68% in comparison to 31% (p<0.001) in the R-CHOP group. Data regarding treatment toxicity were

Table I. *Clinical characteristics at the time of diagnosis according to the administration of the monoclonal antibody rituximab. Except for bone marrow involvement (p=0.014) no statistically significant differences between the R-CHOP and CHOP(-like) group were observed.*

Parameter	R-CHOP (N=219)			CHOP/CHOP-like (N=88)		
	No.	Valid	%	No.	Valid	%
Age >60 years	118	219	54	56	88	64
Median age (range), years		63 (18-90)			67 (18-93)	
M:F	119:100	219	54:46	45:43	88	51:49
Stage I	37	219	17	14	88	15
Stage II	60	219	27	34	88	39
Stage III	45	219	20	18	88	20
Stage IV	77	219	35	22	88	26
IPI≥2	140	198	71	54	87	62
≥2 Extranodal sites	64	209	31	29	86	24
B-Symptoms	78	188	41	32	80	40
LDH >UNL	108	190	57	42	85	49
Performance status >1	49	189	26	25	86	29
Liver disease	18	212	8	-	-	-
β-2-Microglobulin >UNL	65	162	40	-	-	-
Median hemoglobin (range), g/dl		13 (6.7-16.8)		-	-	-
Median WBC (range), /ul		7300 (2200-57000)		-	-	-
Median platelet count (range), /ul		268000 (75000-657000)		-	-	-
Median albumin (range), g/dl		3.7 (1.9-5.3)		-	-	-
Median C-reactive protein (range), mg/dl		1.69 (0-30)		-	-	-
Creatinine mg/dl		0.86 (0.35-3.97)		-	-	-

UNL, Upper normal limit; WBC, white blood cell count; M, male; F, female; LDH, lactate dehydrogenase; IPI, international prognostic index.

Table II. *Treatment cycles, responses, percentages of relapse and death according to administration of rituximab.*

Parameter	R-CHOP (N=219)			CHOP/CHOP-like (N=88)		
	No.	Valid	%	No.	Valid	%
Median therapy cycles, n (range)		6 (1-10)			6 (1-11)	
Complete remission	155	214	72	61	87	70
Partial remission	22	214	10	1	87	1
Stable disease	6	214	3	0	87	0
Progressive disease	18	214	8	18	87	21
Treatment not completed	13	214	6	7	87	8
Relapse	31	153	26	20	59	44
Death	69	219	31	61	88	69

not available. However, it is noteworthy to mention that one patient of the R-CHOP group suffered progressive multi-focal leukencephalopathy (14).

After a median follow-up of 3.5 years (range: 1 month to 12.5 years) and 2.8 years (range: 1 month to 23 years) in the R-CHOP and CHOP group, the 5-year PFS was 56% and 44% (p=0.002), respectively (Figure 1). OS was also significantly longer in the former group, with a 5-year OS of 69% compared to 40% (p<0.001), respectively (Figure 1). To assess the impact of rituximab on outcome in the context of other well-established prognostic parameters, a Cox multivariate analysis was performed considering the whole cohort of DLBCL (281 evaluable cases). The addition of the monoclonal antibody proved to be a strong independent predictor for a prolonged OS (hazard ratio=0.39, 95% confidence interval=0.27-0.56, p<0.001) and PFS (hazard ratio=0.48, 95% confidence interval=0.35-0.68, p<0.001). In order to evaluate whether rituximab improved survival according to the single risk factors of the IPI, we built a second Cox model. OS and PFS were independently

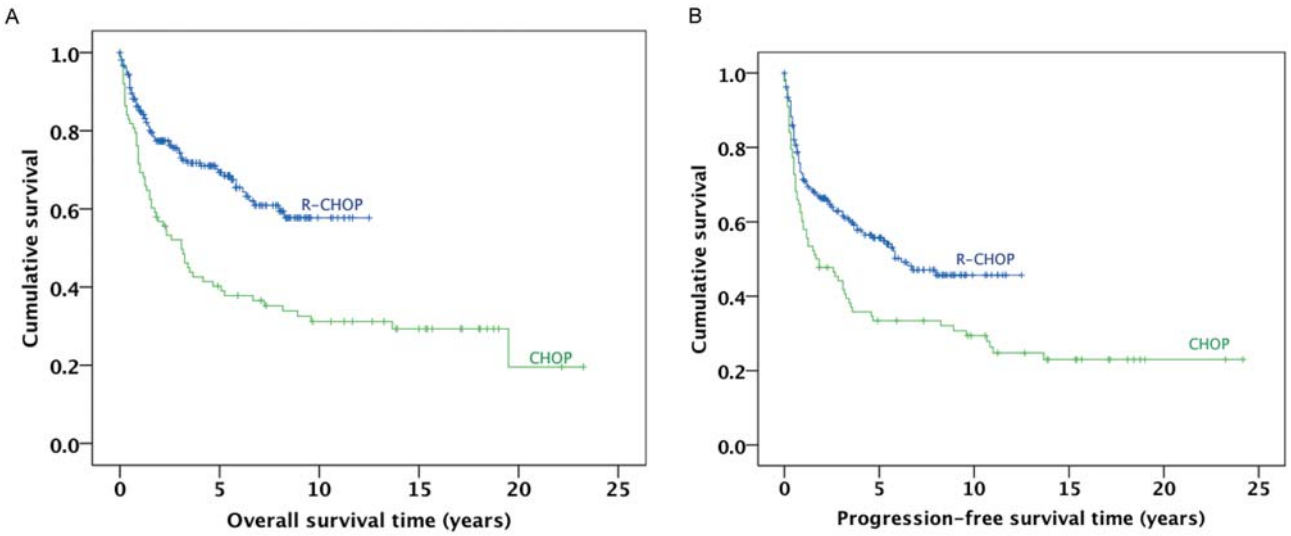

Figure 1. Overall survival (A) and progression free survival (B) according to CHOP (green) or R-CHOP (blue).

prolonged by rituximab in patients patients with age >60 years (OS, $p<0.001$; PFS, $p=0.007$), poor performance status (OS, $p<0.001$; PFS, $p=0.001$) and stage III/IV disease (OS, $p<0.001$; PFS $p=0.001$), while this was not the case for the remaining IPI parameters.

Discussion

In the present work, we clearly demonstrate in a real-life setting of patients with DLBCL that R-CHOP treatment results in high response and long-term remission rates, to an extent that can be expected from prospective trials. Secondly, we show that a number of clinical and laboratory parameters (some of which the classic prognostic systems were established from) nicely predict treatment outcome in the context of routine use of R-CHOP. Finally, we confirm the independent impact of rituximab on the outcome of an unselected population of patients with DLBCL.

The strengths of this registry-based analysis are the extraordinarily long accrual period and follow-up, and the large number of clinical parameters at diagnosis. The main limitation of this study is its retrospective nature and the lack of a central histological revision of the histopathological slides. On the other hand, we were able to show in different neoplasias that prospective treatment results can be confirmed in a real-life setting (4, 5, 15, 16); thus, it is likely that this is also valid in DLBCL. Another limit was that due to the long accrual period, not all patients underwent staging and final response evaluation by PET/CT since it was not yet available in the early years of the accrual period.

After completion of R-CHOP treatment, 72% of the patients achieved a CR. When compared to prospective clinical trials, response rates as observed in our retrospective cohorts were similar to those reported, ranging between 76%-86% (3, 4, 5). Of the population-based analyses (7, 8, 9), only the report from Sweden (6) provided response information, namely 76%.

We evaluated the efficacy of the anti-CD20 agent not only in terms of response and relapse, but also by estimating survival differences in univariate and multivariate analysis. As expected, the 5-year estimated PFS and OS were 56% and 69%, respectively. These results were similar to what was reported in two of the population-based analyses (8, 9), and with the prospective studies (13, 14, 15). Of note, in the rituximab era, in univariate and multivariate analysis, anemia proved to be an independent predictor for shorter OS and PFS. Therefore, a future revision of the IPI should consider hemoglobin below 13 g/dl as a potential additional risk factor.

Comparing the historical CHOP/CHOP-like cohort with the R-CHOP group, clinical parameters assessed at time of diagnosis were similar in both groups, allowing a direct comparison. Unexpectedly, the percentage of CR was similar in both groups. However, it cannot be excluded that response evaluation in the R-CHOP group was more stringent due to availability of PET-CT in the rituximab era. When compared to prospective clinical trials, CR rates as observed in our retrospective cohorts were similar to the 63%-73% previously observed for the CHOP-like group (2, 4, 5). In contrast, the Swedish register study reports a much lower CR/CRu rate of 45% (6). Despite the identical percentage of CR for the

Table III. *Univariate and multivariate analysis of the clinical and laboratory parameters at time of diagnosis for PFS and OS. Abbreviations: HR, hazard ratio; CI, confidence interval.*

Parameter	Number of patients	5-Year PFS (%)	*p*-Value		HR (95% CI)	5-year OS (%)	*p*-Value		HR (95% CI)
			Log-rank	Cox			Log-rank	Cox	
Age									
≤60 years*	99	61	0.076	0.617	1.2 (0.6-2.6)	79	<0.001	0.009	4.3 (1.4-12.6)
>60 years	116	51				61			
Performance status									
<2*	138	76	<0.001	0.378	1.5 (0.6-3.4)	76	<0.001	0.985	1 (0.4-2.6)
≥2	47	53				53			
Extranodal sites									
<2*	143	63	0.003	0.731	1.1 (0.5-2.6)	75	0.018	0.944	1 (0.4-2.6)
≥2	62	40				55			
Stage									
I/II*	96	84	<0.001	0.042	3.1 (1.1-9.1)	85	<0.001	0.188	2.35 (0.7-8.4)
III/IV	119	56				56			
LDH									
≤UNL*	80	69	0.005	0.553	1.3 (0.5-3.5)	81	0.002	0.135	2.7 (0.7-9.9)
>UNL	106	50				62			
IPI									
0-1*	57	78	<0.001	0.626	12.4 (0.3-6.2)	89	<0.001	0.513	1.8 (0.3-11.3)
≥2	137	37				62			
Liver involvement									
No*	191	58	0.019	0.341	1.6 (0.6-4.5)	71	0.050	0.284	2 (0.6-7.2)
Yes	17	38				54			
B-Symptoms									
No*	109	69	0.002	0.455	1.3 (0.6-2.8)	77	0.052	0.465	1.4 (0.6-3.3)
Yes	75	46				64			
Hemoglobin									
≥13 g/dl*	100	68	<0.001	0.046	(1-4.5)	79	0.001	0.206	1.7 (0.7-4.1)
<13 g/dl	89	47				60			
β2-Microglobulin									
≤UNL*	95	73	<0.001	0.934	1 (0.5-2.1)	81	<0.001	0.749	1.2 (0.5-2.8)
>UNL	63	42				55			
Albumin									
≥3.5 g/l*	103	68	0.001	0.664	1.2 (0.5-2.7)	80	<0.001	0.195	1.8 (0.7-4.7)
<3.5 g/l	51	48				52			
C-Reactive protein									
≤5 mg/dl*	143	62	0.001	0.426	1.4 (0.6-3.2)	74	0.002	0.351	1.6 (0.6-4.4)
>5 mg/dl	42	46				57			

UNL, Upper normal limit; LDH, lactate dehydrogenase; IPI, international prognostic index. *markes the referent (HR=1.0).

compared groups, the number of relapses differed significantly. Certainly, this reflects the higher efficacy of the monoclonal antibody in eliminating minimal residual disease, which is known to be a potential cause of disease relapse (19).

To assess the impact of rituximab on outcome after controlling for the IPI, a Cox multivariate analysis encompassing the patients of both cohorts altogether was performed. The addition of the monoclonal antibody proved to be a strong independent predictor for OS and PFS. Again, these results were comparable to previously published data (8, 9). Moreover, this positive effect on OS and PFS was independent of age, performance status and stage of disease. Of note, the higher percentage of patients with stage III/IV disease in the R-CHOP group did not significantly reduce their survival.

In conclusion, in a real-life setting, R-CHOP results in high response and long-term remission rates. We confirm the independent impact of rituximab on the outcome of an unselected population of patients with DLBCL.

Conflicts of Interest

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