ORIGINAL ARTICLE

ADDITION OF RITUXIMAB SIGNIFICANTLY IMPROVES OUTCOMES IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA – A SINGLE-CENTER, RETROSPECTIVE STUDY

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Summary: CHOP chemotherapy has been used as a standard first-line treatment for diffuse large B-cell lymphoma since the 1970s. Phase III trials have shown that the addition of rituximab (R) to CHOP chemotherapy leads to significant improvements in response rate, progression-free survival and overall survival. This single-center, retrospective study was performed to evaluate the role of the addition of R to chemotherapy (CHT) in a real-world clinical setting. Outcomes were assessed in 85 patients with newly diagnosed DLBCL treated with CHT alone (n=38) and R-CHT (n=47). Complete response (CR) rates were significantly higher after R-CHT than CHT (93 % vs. 73 %; p=0.02). The relapse rate was significantly higher after CHT compared with R-CHT (38 % versus 12 %; p=0.01). Progression-free survival was significantly extended by the addition of R (median not reached versus 26.1 months; p=0.04). These data bring further support for rituximab-based immunochemotherapy as a standard first-line therapy for patients with DLBCL.

Key words: *Diffuse large B-cell lymphoma; Rituximab; Non-Hodgkin's lymphoma; Immunochemotherapy*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), accounting for 35 % of newly diagnosed lymphomas (26). The majority of patients have systemic disease at the time of diagnosis and require chemotherapy. Since the introduction of anthracycline-based chemotherapy in the 1970s, DLBCL has been considered a potentially curable disease (9). The CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen has been accepted as standard chemotherapy for patients with DLBCL for over 25 years, principally on the basis of the SWOG-8516 trial, which showed no benefit after intensification of therapy (4,11).

The introduction of rituximab represents a major breakthrough in the treatment of patients with DLBCL. Rituximab (Rituxan®, Genentech/Biogen Idec; MabThera®, F. Hoffmann-La Roche AG) is a chimeric IgG1 monoclonal antibody that specifically binds to the CD20 B cell surface antigen. Its mechanisms of action are multiple and include complement-mediated lysis, antibody-dependent cytotoxicity, and induction of apoptosis (1,2,12,13). The US Food and Drug Administration approved Rituximab in 1997 for patients with relapsed and refractory follicular lymphoma (17). Early studies also indicated that rituximab monotherapy was active and well tolerated in patients with relapsed or refractory DLBCL (7).

A Phase II study of rituximab plus CHOP (R-CHOP) as first-line treatment of 33 patients with aggressive NHL yielded an overall response rate (ORR) of 94 %, with 61 % complete responses (CR) (28). Long-term follow-up indicated that the remissions achieved were durable – at 5 years, progression-free survival (PFS) and overall survival (OS) rates were 87 % and 80 %, respectively (27). In the pivotal, randomized Groupe d'Etude des Lymphomes de L'Adulte (GELA) LNH 98–5 trial conducted in elderly patients with previously untreated DLBCL, the addition of rituximab to CHOP resulted in significant improvements in the CR rate, which translated into significantly prolonged PFS, event-free survival (EFS), and OS (5,6,7). Importantly, the improvements in clinical outcome were achieved without any clinically significant increase in toxicity. The survival benefit for R-CHOP was maintained at the 5-year follow-up (10). These impressive results led to the establishment of R-CHOP as a standard first-line treatment for patients with DLBCL.

Further studies have supported the clinical utility of combining rituximab with CHOP and CHOP-like chemo-

therapy in the treatment of newly diagnosed DLBCL, in younger as well as older patients (14,15,18,23). ECOG 4494 was a Phase III study that in the first randomization evaluated the safety and efficacy of R-CHOP versus CHOP induction in elderly patients with previously untreated DLBCL and in a second randomization evaluated the efficacy of subsequent rituximab maintenance therapy in patients responding to induction (14–15). The 3-year failure-free survival (FFS) rate was significantly higher after R-CHOP ± maintenance versus CHOP ± maintenance (53 % versus 46 %; p=0.04), and after using weighted Cox's regression analysis to remove the confounding effect of maintenance therapy, both FFS and OS were significantly improved after R-CHOP induction compared with CHOP alone (3-year FFS: 52 % versus 39 %; p=0.003; 3-year OS: 67 % versus 57 %; p=0.05). By contrast, preliminary data from a Phase II study of rituximab-containing chemotherapy induction followed by rituximab maintenance in a similar group of patients produced a 2-year PFS rate of 90 %, suggesting a potential role for rituximab maintenance after R-chemotherapy in this context (22).

Here we report on a retrospective analysis conducted to determine the clinical benefit conferred by the addition of rituximab to CHOP or other chemotherapy in patients newly diagnosed with DLBCL treated at the Charles University Hospital, Hradec Králové, Czech Republic, between January 2001 and November 2004.

Patients and methods

Study design. This was a retrospective study evaluating the role of adding rituximab to anthracycline-based chemotherapy in patients with newly diagnosed DLBCL. Patients were treated at the Hematology Department of Charles University Teaching Hospital in Hradec Králové between January 2001 and November 2004. The analysis was performed in March 2006, giving a minimum follow-up of 12 months from the data of termination of the last patient's therapy. This analysis compares two historically different treatment strategies (chemotherapy (CHT) alone versus rituximab plus CHT (R-CHT) used in the periods before and after September 2002, when rituximab was introduced at our institution for the treatment of newly diagnosed DLBCL.

Eligibility criteria. All patients with newly diagnosed, histologically verified DLBCL who were treated with CHOP or other anthracycline-based CHT with or without rituximab with curative intent were included in the analysis. Patients with primary central nervous system lymphoma were excluded from the analysis, owing to the lack of information on the efficacy of rituximab in this setting and the poor prognosis compared with other patients with DLCBL (24). Patients with localized disease treated with radiotherapy only were also excluded.

Treatment. All patients received anthracycline-based chemotherapy. Patients treated with CHOP-21 alone received a combination of cyclophosphamide, vincristine, doxorubicin, and prednisone at standard doses every 21 days. Other anthracycline-based chemotherapy regimens administered were MegaCHOP/ESAP/BEAM (intensified CHOP/etoposide, methylprednisolone, cytarabine/carmustine, cytarabine, etoposide, melphalan), hyperCVAD/HD-MTX + Ara-C (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone/high-dose methotrexate and cytarabine), and VACOP-B (vincristine, doxorubicin, cyclophosphamide, etoposide, prednisone, bleomycin). Patients treated with R-CHT received rituximab 375 mg/m^2 intravenously on Day 1 of each cycle. Treatment was repeated every 21 days for a median of 6 (range 6–8) cycles.

Assessment of response. Efficacy variables including response rate and PFS were used to compare the CHT and R-CHT treatment schedules. Response criteria were used according to the report of the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (3). PFS was defined as the time from the date of diagnosis to documented disease progression and OS as the time from diagnosis until death from any cause.

Patients were followed up every 3 months after completion of therapy for the first 2 years and every 6 months thereafter. Routine examination of disease activity (computed tomography (CT) scan) was performed every 6 months in the first year and then once a year, or in the case of relapse/progression. Patients who relapsed/progressed were treated according to local clinical practice.

Toxicity. Toxicity of the treatments was assessed according to the standardized National Cancer Institute Common Toxicity Criteria, version 3.0.

Statistical analysis. Rituximab in combination with CHOP therapy was introduced into the first-line treatment of patients with DLBCL in the Czech Republic in September 2002. The analysis is based on follow-up data up to November 2005. Clinical and laboratory characteristics of patients treated with CHT only and R-CHT were compared.

Data were assessed according to the intention-to-treat principle; patients who received at least one cycle of therapy were included in the analysis. OS and PFS were estimated using the Kaplan–Meier method (15). Comparison of survival curves was performed using the log-rank test. Fisher's exact test was used for statistical analysis of variables between CHT and R-CHT groups. Data were analyzed using NCSS statistical software version 6.0.

Results

Patient characteristics. The analysis included 85 patients with newly diagnosed DLBCL (48 patients in the R-CHT group and 37 patients in the CHT group) with a median age of 59 years (range 20–81 years). Initial stage I/II/III/IV disease was found in 17/33/16/19 patients, respectively. Classification according to the International Prognostic Index (IPI) score showed that the majority of patients (65 %) had an IPI score of 2–5. Elevated lactate dehydrogenase

(LDH) was present at the time of diagnosis in 64 patients (75 %), extranodal involvement in 53 patients (62 %), and bulky disease >7 cm in 34 patients (40 %). The mediastinal variant of DLBCL was diagnosed in 14 cases (16 %). All patients were confirmed as having CD20-positive disease by immunohistochemistry. Treatment groups (CHT and R-CHT) were well balanced with respect to disease stage, extranodal involvement, IPI score, and age (Tab. 1).

All patients received anthracycline-based chemotherapy. CHOP-21 with or without rituximab was given to 63 patients (74 %). Twenty patients (24 %) were treated with the MegaCHOP/ESAP/BEAM regimen with or without rituximab within a Phase II study of the Czech Lymphoma Study Group for patients under 65 years with intermediate- and high-risk DLBCL (21). One patient received hyper-CVAD/HD-MTX+Ara-C and one VACOP-B plus rituximab. Treatment groups were well balanced with respect to first-line treatment regimen and proportion of patients treated with the high-dose protocol (MegaCHOP/ESAP/BEAM with or without rituximab) (Tab. 2). Although rituximab was introduced for the treatment of patients with DLBCL in the Czech Republic in September 2002, 4 patients (14 %) received it before this date. In addition, 13 patients (23 %) were treated with chemotherapy only in the "early rituximab era."

Treatment response. At the time of reporting, 85 patients were evaluable for efficacy, 48 in the R-CHT group and 37 in the CHT group. Median follow-up for living patients was 31 months for the whole group (range 10–54 months), 21 months (range 10–33 months) in the R-CHT group, and 38.5 months (range 29–54 months) in the CHT arm.

Complete remissions were observed more frequently with R-CHT than with CHT (CR + CRu: 93 % versus 73 %, p=0.02) (Tab. 3). Multivariate analysis revealed administration of rituximab with CHT, low IPI (0/1), and stage I/II disease were all strong predictors of CR achievement after initial treatment (Tab. 4).

The rate of relapse or disease progression was significantly higher after CHT than R-CHT therapy (38 % versus 12 %; p=0.01) (Tab. 3). There was also a significantly lower incidence of early relapses (i.e. within 12 months) in the R-CHT arm compared with the CHT arm (8 % versus 34 %; p=0.03) (Tab. 3). Median time to disease progression or relapse was 10.5 months for all patients (range 6–28 months). The addition of rituximab to chemotherapy resulted in significantly better PFS – median PFS was significantly increased in the R-CHT group compared with the

Tab. 1: Patient characteristics in each treatment arm.

Characteristic	R-CHT (n=48)	CHT (n=37)	p-value
Median age, years (range)	55 (22–82)	63 (20–81)	0.08
Male, %	62	59	0.82
Stage III/IV, %	48	32	0.19
IPI score, %			
0–1	33	40	0.51
2–5	67	60	0.51
Elevated LDH, %	83	65	0.08
Primary mediastinal DLBCL, %	21	11	0.25
Bulky disease >7 cm, %	50	27	0.05
Extranodal involvement, %	56	70	0.26

CHT – anthracycline-based chemotherapy; DLBCL – diffuse large B-cell lymphoma: IPI – International Prognostic Index; LDH – lactate dehydrogenase; R – rituximab

Tab. 2: Type of first-line chemotherapy administered.

	R-CHT (n=48)	CHT (n=37)	p-value
CHOP-21 ± R, %	69	81	0.22
MegaCHOP/ESAP/ BEAM ± R, %	29	16	0.20
Hyper-CVAD/HD MTX-Ara-C, %	0	3	NA
VACOP-B + R, %	2	0	NA

Doses and Schedules:

CHOP-21: Cyclophosphamide 750 mg/m^2 IV D1, doxorubicin 50 mg/m^2 IV D1, vincristine 1.4 mg/m^2 IV D1 (maximum 2 mg), prednisone 100 mg PO D1–5

MegaCHOP: Cyclophosphamide 3000 mg/m^2 IV D1 (with mesna prophylaxis 3000 mg/m^2), doxorubicin 75 mg/m^2 IV D1, vincristine 1.4 mg/m^2 IV D1 (maximum dose 2 mg), prednisone 100 mg D1–5 + filgrastim 5 μg/kg/day started D6

ESAP: Etoposide 60 mg/m^2 IV D1–4, cisplatin 25 mg/m^2 IVCI D1–4, cytarabine 2 g/m^2 IV D5, methylprednisolone 500 mg IV D1–4

BEAM: Carmustine 300 mg/m^2 IV D-7, etoposide 300 mg/m^2 IV D-7 to -4, cytarabine 400 mg/m^2 IV D-7 to -4, melphalan 140 mg/m^2 IV D-3

Hyper-CVAD: Cyclophosphamide 300 mg/m^2 IV q 12 h D1–3, doxorubicin 16.6 mg/m^2 IVCI over 72 h D 4–5, vincristine 1.4 mg/m^2 IV D5+12 (maximum 2 mg), dexamethasone 40 mg IV or PO D1–4 and D11–14 + G-CSF 5 μg/kg/day started D7

MTX-Ara-C: Methotrexate 200 mg/m^2 IV over 2 h D1, methotrexate 800 mg/m^2 IVCI over 22 h D1, cytarabine 3 g/m^2 IV over 2 h q 12 h x 4 D2–3 + G-CSF 5 μg/kg/day started D4

VACOP B: Doxorubicin 50 mg/m^2 IV D1 wk 1, 3, 5, 7, 9, 11, cyclophosphamide 350 mg/m^2 IV D1 wk 1, 5, 9, vincristine 1.2 mg/m^2 IV (maximum dose 2 mg) IV D1 wk 2, 4, 6, 8, 10, 12, bleomycin 10 mg/m^2 IV D1 wk 2, 4, 6, 8, 10, 12, etoposide 50 mg/m^2 IV D1 and 100 mg/m^2 D 2–3 wk 3, 7, 11

CHT – anthracycline-based chemotherapy; D – day; IV – intravenously; IVCI – intravenously as continuous infusion; MTX – methotrexate; NA – not applicable; PO – per os; q – every; R – rituximab

Tab. 3: Clinical outcomes according to treatment arm.

Outcome	Rate (%)		
	R-CHT (n=48)	CHT (n=37)	p-value
Cru + CR	93	73	0.02
Any events	23	43	0.05
Relapse/progression	12	38	0.01
Relapse/progression < 12 months	8	34	0.02
Death	15	30	0.11
2-year PFS	82	55	0.04

CHT – anthracycline-based chemotherapy; CR – complete response; CRu – complete response, unconfirmed; PFS – progression-free survival; R – rituximab

Tab. 4: CR/CRu after first-line treatment.

Characteristic		CR/CRu rate (%)	p-value
Stage I/II disease	*Yes*	93	
	No	73	0.02
Elevated serum LDH	*Yes*	86	
	No	84	1.0
IPI 0/1	*Yes*	97	
	No	78	0.02
Bulky disease >7 cm	*Yes*	83	
	No	86	0.75
Primary mediastinal DLBCL	*Yes*	90	
	No	84	0.70
Extranodal involvement	*Yes*	80	
	No	93	0.12
Rituximab in initial therapy	*Yes*	93	
	No	73	0.02
Use of radiotherapy	*Yes*	81	
	No	87	0.74
First-line HDT with ASCT	*Yes*	85	
	No	84	1.0

ASCT – autologous stem cell transplantation; CR – complete remission; CRu – complete remission unconfirmed; DLBCL – diffuse large B-cell lymphoma; HDT – high-dose therapy; IPI – International Prognostic Index; LDH – lactate dehydrogenase.

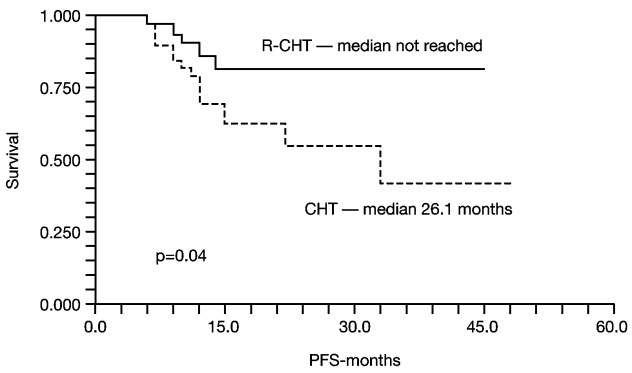

Fig. 1:. Kaplan–Meier curves of progression-free survival according to treatment (R-CHT or CHT).

CHT group (median not reached versus 26.1 months; p=0.04) (Fig. 1). Despite the trend to prolonged overall survival in R-CHT arm, the difference was not statistically significant at the time of assessment. Nineteen of twenty patients received further treatment at relapse or disease progression. Nine received palliative therapy, 6 patients were treated with salvage chemotherapy (R-ICE or R-ESAP) and 4 received salvage chemotherapy (R-ICE) followed by high-dose chemotherapy and autologous stem cell transplantation. Seven patients responded to second-line therapy, yielding an ORR of 37 % (6 CRs and 1 PR). The actuarial 2-year PFS and OS rates for the entire group were 65 % and 84 %, respectively.

Toxicity. The predominant toxicity was hematologic (Tab. 5). Grade 3 and 4 thrombocytopenia and neutropenia occurred in 34 % and 38 % of patients, respectively. The majority of observed toxicities were seen in patients receiving the MegaCHOP/ESAP regimen with or without rituximab with autologous stem cell transplantation. Neutropenic fever occurred in 25 % and 19 % of patients in the R-CHT and CHT arms, respectively. All of these patients were treated with the intensive protocol described above. There were 10 grade 3/4 infections – 5 in each arm – comprising 7 cases of pneumonias (two of them of fungal origin), 2 cases of severe neutropenic sepsis, and 1 central venous catheter sepsis. Other common toxicities included nausea and/or vomiting (grade 3/4 in 12 % of patients). Venous thromboembolism occurred in 4 patients, and 1 patient developed dilation cardiomyopathy, probably related to anthracycline therapy. There were no statistically significant differences between the R-CHT and CHT groups in terms of the main toxicities observed (Tab. 5).

Tab. 5: Toxicities by treatment arm.

Toxicity	R-CHT (n=48)	CHT (n=37)	p-value
	Rate (%)		
Thrombocytopenia 3/4 grade	39	30	0.49
Neutropenia grade 3/4	37	40	0.82
Neutropenic fever	25	19	0.60
Nausea/vomiting, grade 3/4	13	12	1.0
	No. of events		
Infection			
Pneumonia	4	3	
Bacteremia	1	2	
Other			
Deep venous thrombosis	2	2	
Myocardial infarction	0	1	
Dilatation cardiomyopathy	1	0	

CHT – anthracycline-based chemotherapy; R – rituximab

Discussion

The treatment outcome for patients with DLBCL has dramatically improved since the addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy protocols. The major benefit of rituximab lies in its ability to improve efficacy with no significant additional toxicity. Many studies have been conducted to assess the potential benefits of rituximab-based chemoimmunotherapy. In the pivotal GELA LNH 98-5 trial in elderly patients with previously untreated DLBCL, the addition of rituximab to CHOP conferred a significant improvement in complete response rate and EFS as well as in overall survival (5,6,7). The improvements in clinical outcomes, including overall survival benefit, were maintained at the 5-year follow-up (10).

Results of the MabThera International Trial (MInT) support the clinical utility of the addition of rituximab to CHOP and CHOP-like chemotherapy in newly diagnosed aggressive NHL in low-risk patients aged 60 and under 60 (18). The British Columbia population-based retrospective analysis has shown that patients treated in the "rituximab era" had an 18 % improvement in 2-year PFS and 25 % improvement in 2-year OS compared with those in the "pre-rituximab era." The period of treatment was an independent strong predictor of outcome, with respect to better PFS and OS, for patients in the "rituximab era" (23). Although the results of the ECOG 4494 study of R-CHOP versus CHOP in elderly patients with DLBCL were less clear-cut, this is likely to be a result of the confounding effects of maintenance therapy and possibly the different administration schedules used (8 cycles of rituximab and CHOP in the GELA study compared with 4-5 cycles of rituximab and 6-8 cycles of CHOP in ECOG 4494) (14-15).

The benefit of adding rituximab to chemotherapy in younger intermediate- and high-risk (age-adjusted IPI 2-3) patients under 60 years of age remains unproven. The optimal intensity of chemotherapy also remains unclear. Pfreundschuh and colleagues have conducted a study evaluating dose and/or time intensification of CHOP by shortening treatment intervals from 3 to 2 weeks (CHOP-14) and/or adding etoposide to CHOP (CHOEP) in patients with aggressive lymphoma. Time intensification significantly improved the time to treatment failure in patients 60 years of age and older (19). The RICOVER-60 trial has investigated the addition of 8 cycles of rituximab to 6 or 8 cycles of CHOP-14 in comparison with 6 or 8 cycles of CHOP-14 alone (20). Preliminary results show that the addition of 8 doses of rituximab to 6 cycles of CHOP-14 is associated with an optimal outcome in patients newly diagnosed with DLBCL over 60 years old. No benefit of 8 cycles of CHOP-14 chemotherapy has been shown in comparison with 6 cycles of CHOP-14 (20).

Our retrospective analysis was performed to evaluate the clinical benefit of the addition of rituximab to CHOP or other anthracycline-based chemotherapy in the first-line treatment of patients with DLBCL. Although this study is not a concurrent comparison or randomized trial, our results support the essential role of rituximab-based chemoimmunotherapy in improving clinical outcomes in patients with DLBCL. The addition of rituximab to chemotherapy yielded an improved CR rate compared with chemotherapy alone. The increased response rate with R-CHT translated into a PFS benefit. R-CHT was associated with significantly prolonged PFS compared with CHT alone. Although longer follow-up is required to determine any overall survival benefit, these data lend further support to the clinical utility of the addition of rituximab to chemotherapy for the first-line management of DLBCL in routine clinical practice.

Results of ongoing randomized trials are expected to answer some key questions, including the most appropriate chemotherapy regimen to be combined with rituximab, the optimal timing, the level of dose to be administered, and the duration of therapy for individual patients (25). Many questions are still to be answered in this field, but the combination of rituximab and chemotherapy is generally accepted as the current standard for all patients with newly diagnosed DLBCL. The addition of rituximab to chemotherapy presents a milestone in the treatment of patients with DLBCL in the last 20 years.

Acknowledgements

This work was supported by research project MZO 00179906 from Ministry of Health, Czech Republic, and by grant NR 8231-3/2004 from Internal Grant Agency, Ministry of Health, Czech Republic.

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Submitted March 2007.
Accepted May 2007.

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