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SPECIAL REPORT

Improved survival for patients with large B-cell lymphoma after introduction of rituximab

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ABSTRACT

Background: To determine whether the reported increase in survival of patients with diffuse large B-cell malignant lymphoma (DLBCL) after the introduction of rituximab is also seen in a non-academic hospital in the Netherlands. A retrospective study.

Methods: A dataset was made containing all newly diagnosed patients with DLBCL in a period of 2.5 years before until 2.5 years after introduction of rituximab in the standard treatment. Total follow-up time was 6.5 years with a minimal follow-up of 18 months.

Results: The study population consisted of 65 patients; 32 in the prerituximab group (median follow-up time 60 months) and 33 in the postrituximab group (median follow-up time 29 months). Progression-free survival increased significantly in the postrituximab group (hazard ratio 0.31; 95% CI 0.12 to 0.78; p=0.013; log rank p=0.008). The overall survival also showed a significant increase (p=0.048). The 18-month progression-free survival increased from 59.4 to 81.8%; the overall survival at 18 months showed an increase from 65.5 to 81.8%.

Conclusion: The introduction of rituximab in the treatment of DLBCL with CHOP chemotherapy has resulted in a significantly better prognosis for patients with DLBCL, treated in the Reinier de Graaf Gasthuis in Delft.

KEYWORDS

Diffuse large B-cell malignant lymphoma (DLBCL), (R-) CHOP, rituximab

INTRODUCTION

Diffuse large B-cell malignant lymphoma (DLBCL) is the most prevalent form of malignant lymphoma and accounts for 30 to 40% of cases.[1,2] Mean age at clinical presentation is 65 years and more than 60% of patients are aged ≥60 years at the time of diagnosis.[3,4] Extranodal manifestation occurs in 40% of patients.[5]

In the group of DLBCL various subtypes are discernable, so far, however, without consequences for therapeutic choices.[1,6]

Since the mid-1970s DLBCL has been treated with combination chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone: CHOP chemotherapy.[7,8]

More intensive treatment schemes were used later on, but a randomised trial did not show improvement for these regimens in comparison with the classical CHOP scheme.[7]

An approximation of prognosis can be made using the International Prognostic Index (IPI). Depending on the IPI score, five-year survival varied between 26 and 73% in the era of CHOP chemotherapy.[4]

Rituximab has been registered in Europe since 1998. It is a monoclonal antibody against the pan-B-cell antigen CD20.[9] Since the introduction of rituximab (R-CHOP) a revolutionary improvement in treatment outcome was achieved, especially in the low-risk group according to IPI. Several studies have shown better results in progression-free and total survival after the addition of rituximab to CHOP treatment.[10-15] The British Columbian study showed a four-year progression-free survival of 53 to 94% and a four-year survival of 55 to 94% with R-CHOP, depending on the IPI score.[10]

Using the study from British Columbia as a background, we analysed the treatment results in our clinic.

MATERIALS AND METHODS

The retrospectively formed database consisted of information on patients, included if the time of diagnosis was between February 2001 and February 2006; that is 2.5 years before and 2.5 years after the introduction of rituximab in treatment of DLBCL in our clinic.

Follow-up was achieved until September 2007 with a minimal follow-up time of 1.5 years and a maximum of 6.5 years. Thanks to the cancer registry department of the Comprehensive Cancer Centre West patients could be identified for inclusion in our study.

Treatment consisted of CHOP in standard dosage every three weeks: three cycles for stage one (in exceptional cases four cycles) and six to eight cycles for stage II-IV, depending on disease aggressiveness. Rituximab was administered in standard dosage, 375 mg/m^2, in every CHOP cycle.

In stage I disease, involved-field radiotherapy was given after the three cycles of chemotherapy. In stage II-IV disease, radiotherapy was only given in exceptional cases, in doubt about the chance of complete remission. G-CSF support was not used in a standard way, only by indication.

All patients were discussed in a regional meeting of the Comprehensive Cancer Centre West. In case of doubt about the diagnosis, pathology was reconsidered by the lymphoma panel of pathologists.

Revised International Prognostic Index (r-IPI) was used for prognostic determination, with risk factors: age over 60 years, Ann Arbor stage III/IV, increased lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status ≥2 and more than one extranodal manifestation.[4,16] Only nine patients scored no risk factors: four in the CHOP group and five in the R-CHOP group. For this reason we created two risk categories according to r-IPI: low-risk (0-2 risk factors present) and high-risk (3-5 risk factors present).

We analysed the prerituximab and postrituximab group for progression-free survival and overall survival, followed by analysis on survival per risk group.

Patients were excluded in case of central nerve system localisation of the disease at time of presentation, HIV positivity or in case of transformation from indolent lymphoma.

STATISTICAL ANALYSIS

Prognostic variables were compared using the unpaired t-test for numerical variables and χ^2 test for categorical variables. Time until progression of disease was defined as time between start of treatment and disease progression, relapse or death. Time until death was defined as time between first treatment and death.

Differences in progression free survival (PFS) and overall survival (OS) between the two groups were analysed using the Kaplan-Meier method and Cox regression analysis. The log-rank test was used to compare the Kaplan-Meier curves. Cox regression was used for analysis after stratification for risk group, according to r-IPI. Data were analysed using 'Statistical Software Package for the Social Sciences' (SPSS version 15.0).

RESULTS

Sixty-five patients were included with onset of disease between February 2001 and February 2006, of which 32 belonged to the prerituximab group and 33 to the postrituximab group. Median age was 69 years for the total patient population, with a range of 29 to 84 years and a mean age of 65 years. Clinical characteristics at time of diagnosis are listed in *table 1*. Although no significant differences were found between the two groups, the postrituximab group contained more males, more often showed stage I/II disease and low-risk according to r-IPI, were less often treated with radiotherapy (RT) and less frequently received G-CSF support. The differences in RT can be explained due to the lower number of patients with stage I disease in the postrituximab group.

The first R-CHOP chemotherapy was administered in August 2003. This date was set as the start of the rituximab era. In the postrituximab group, 88% of the patients were actually treated with rituximab. The number of cycles of chemotherapy varied between three and eight. Four patients had not been able to tolerate the entire therapy due to premature death; two patients in the prerituximab group due to progressive disease and two patients in the postrituximab group due to fatal infection.

The number of cycles of chemotherapy did not differ significantly between the two groups (p=0.301). Median follow-up time was 60 months in the prerituximab group (range 49 to 78 months) and 29 months in the postrituximab group (range 18 to 46 months). No significant difference in relevant factors (r-IPI, age and

Table 1. *Patient characteristics*

Characteristics	Prerituximab (n=32)	Postrituximab (n=33)	P value
Median age, years	67 (range 33-78)	69 (range 29-84)	0.300
Sex:			
• Male	17	23	0.170
• Female	15	10	
Nodal	22	22	0.857
Stage I/II	15	20	0.267
Stage III/IV	17	13	
Low risk (r-IPI 0-2)	20	26	0.149
High risk (r-IPI 3-5)	12	7	
LDH level:			
• Normal	15	18	0.525
• Elevated	16	15	
• Unknown	1	0	
Radiotherapy:			
• Yes	15	8	0.098
• No	16	21	
• Unknown	1	4	
G-CSF support:			
• Yes	11	4	0.053
• No	20	25	
• Unknown	1	4	

stage) was found between the two eras. Disease progression occurred in 18 patients in the prerituximab group (56.3%) against six patients in the postrituximab group (18.2%).

PFS increased significantly in the postrituximab group as compared with the prerituximab group (hazard ratio 0.31; 95% CI 0.12 to 0.78; p=0.013; log-rank p=0.008), see *figure 1*.

Progression-free survival at 18 months increased from 59.4 to 81.8% after the introduction of rituximab in the CHOP regimen. Also, OS increased significantly in the postrituximab group as compared with the prerituximab group (hazard ratio 0.39; 95% CI ow.15 to 1.03; p=0.057; log rank p=0.048), see *figure 2*. OS at 18 months increased from 62.5 to 81.8% after introduction of rituximab. Overall, 16 patients died in the prerituximab group compared with six in the postrituximab group. In the prerituximab group all deaths were related to the disease; in the postrituximab group two patients died due to the treatment, the other four due to the disease itself, see *table 2*.

Stratified analysis for risk group showed an improvement in PFS in both risk groups, but significance was only achieved in the low-risk group (low-risk group: hazard ratio 0.23; 95% CI 0.062 to 0.833; p=0.025; high-risk group: hazard ratio 0.73; 95% CI 0.193 to 2.785; p=0.648).

Figure 1. *Progression-free survival (log rank test p=0.008)*

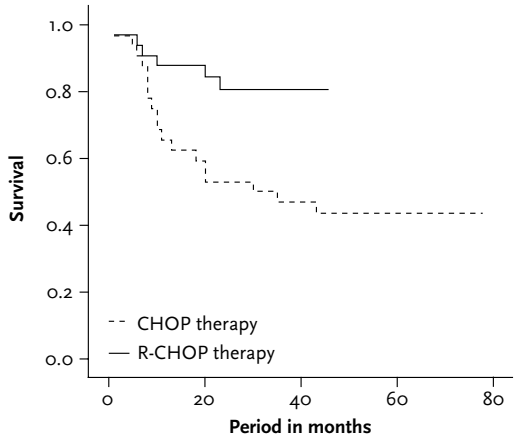

Figure 2. *Overall survival (log rank test p=0.048)*

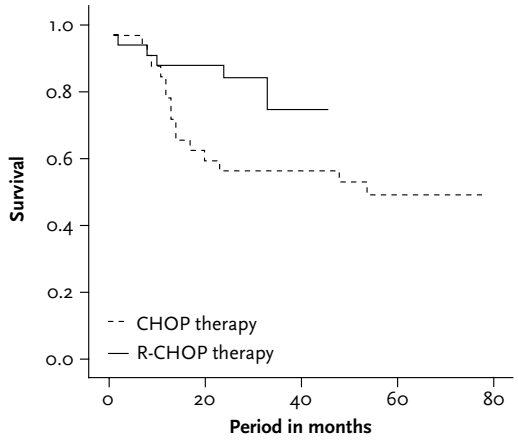

Table 2. *Survival at the end of the study period*

	Prerituximab (%)	Postrituximab (%)
Total no of patients (n= 65)	32	33
Alive without lymphoma	14 (44)	27 (81)
Alive with lymphoma	2 (6)	0 (0)
Died:	16 (50)	6 (18)
• Related to disease	16 (50)	4 (12)
• Related to treatment	0	2 (6)

DISCUSSION

Since rituximab has been introduced in the treatment of diffuse large B-cell malignant lymphoma (DLBCL) the prognosis has improved considerably. Both PFS and OS have increased significantly.[10-15,17]

This study shows the results of this new treatment with respect to PFS and OS of patients with DLBCL in the Reinier de Graaf Gasthuis in Delft since its introduction in our hospital in August 2003. The improvement of PFS (HR 0.31; p=0.008) approaches the improvement shown in the study by Sehn *et al.*[10] In this retrospective Canadian study, improvement of PFS (HR 0.56; p=0.002) and of OS (HR 0.40; p<0.0001) was shown after switching CHOP to R-CHOP. Two year PFS increased from 51 to 69% and two-year OS increased from 52 to 78%.

The first phase III randomised trial was the study by Coiffier *et al.*[11] in the elderly (age 60-80 years). Both two-year PFS (38 and 57% in CHOP and R-CHOP group respectively; HR 0.58) and two-year OS (57 and 70% in CHOP and R-CHOP group respectively; HR 0.64) had improved significantly. Five-year follow-up results confirmed this improvement of treatment.[17]

Confirmation of better treatment results with rituximab in the elderly was done by the US Intergroup (three-year PFS 35 *vs* 52% (HR 0.64) and three-year OS 58 *vs* 67% (HR 0.72) for CHOP and R-CHOP respectively).[12]

Pfreundschuh *et al.* compared treatment results within the younger population (age 18-60 years) in the MInT trial (MabThera International Trial).[14] This younger population also showed a significant increase in survival after the addition of rituximab to the chemotherapy treatment (three-year PFS 68 and 85% (HR 0.42) and three-year OS 84 and 93% (HR 0.40) in CHOP and R-CHOP respectively).

In the underlying study, especially patients with low risk according to r-IPI showed a large improvement in survival after the introduction of rituximab: HR 0.23 *vs* HR 0.73 in high-risk patients according to r-IPI. Feugier *et al.* also showed confinement of improvement especially to low-risk patients according to IPI: low-risk five-year progression-free survival 34 *vs* 69%; high-risk 29 *vs* 47% for CHOP and R-CHOP, respectively.[17]

New developments concern shortening of the interval between chemotherapy cycles from three (R-CHOP-21) to two weeks (R-CHOP-14), as has been investigated in the HOVON-46 and RICOVER-60 trials.[13,15] However, whether R-CHOP-14 is superior to R-CHOP-21 is still under study in randomised trials in France and the United Kingdom. Furthermore, within HOVON (HematoOncologieVOlwassenenNederland) the value of maintenance therapy with rituximab is being studied in the HOVON-84 study.[18]

This study shows the results of difference in treatment outcome between the two eras, before and after the introduction of rituximab. Limitations are the small number of patients per group, the slight imbalance in prognostic characteristics between the groups and the uneven follow-up periods. Bias may have occurred in the patients who were included in the postrituximab group and did not receive rituximab, but outcome for the postrituximab group could probably have been better, if these patients had been treated with rituximab.

The fact that two patients in the postrituximab group died due to infection is challenging. Is there a negative role for rituximab due to B-cell depletion? The small number of patients preclude definitive conclusions and further investigations are required to give more insight into infectious complications due to rituximab.

CONCLUSION

Treatment of patients with DLBCL in daily practice in the Reinier de Graaf Gasthuis confirms the results of better treatment outcome after addition of rituximab, as described in the literature.

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