Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomized controlled trial

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ORIGINAL ARTICLE

Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomized controlled trial

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Abstract The introduction of rituximab into the primary treatment of malignant lymphomas of the B cell lineage has had a major impact on the management of these diseases. In addition, prolonged exposure to rituximab as maintenance therapy has been beneficial in patients with follicular lymphoma and mantle cell lymphoma. For the individual patient, the effect of any prolonged antitumor therapy on the quality of life (QoL) is a very important question. However, so far, the question whether rituximab maintenance therapy may impair QoL in patients with non-Hodgkin's lymphoma remains unanswered. To investigate this subject, we have performed a prospective randomized trial of rituximab maintenance therapy (8 cycles rituximab 375 mg/m^2 every 3 months) versus observation in patients with CD20+B cell non-Hodgkin's lymphoma in our institution. Between July 2002 and December 2005, 122 patients were included into the trial. QoL was assessed with the standardized questionnaires EORTC-QLQ-C30, EuroQol-5D, and EuroQol-5D (VAS) in 91 patients. After statistical analysis with the exact Wilcoxon rank sum test, we found no significant differences of the QoL between the rituximab treatment group and the observation group. We conclude that rituximab maintenance therapy seems to be safe and does not impair quality of life in this patient population.

Keywords Lymphoma · Rituximab · Maintenance · Quality of life

Introduction

Rituximab (R) is a chimeric murine/human anti-CD20 monoclonal antibody capable of killing CD20$^+$ lymphoma cells. Effector mechanisms include complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, and possibly direct induction of apoptosis [1, 2]. In diffuse large B cell lymphomas (DLBCLs) and follicular lymphomas (FLs), several multicenter prospective randomized trials consistently demonstrated an improved outcome when R was added to chemotherapy [3–10]. In FL and DLBCL, it was attempted to further prolong response duration and survival by administering R during remission as maintenance therapy. In DLBCL, Habermann et al. [6] performed a study in patients 60 years of age and older who were initially randomized for chemotherapy with cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) versus CHOP plus R (R-CHOP). Responding

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patients underwent a second randomization for R maintenance versus observation only. In patients receiving R maintenance, a significant prolongation of the time to treatment failure was observed. This beneficial effect was restricted, however, to patients who had received CHOP alone for initial therapy, while in R-CHOP-treated cases, no differences in response duration were found [6]. Currently, the question whether rituximab maintenance is beneficial in diffuse large B cell lymphoma is examined in another large prospective, international randomized trial [11]. Hochster et al. [12] reported a significant prolongation of response duration and even survival by R maintenance in patients with previously untreated advanced-stage FL responding to initial therapy without R comprising chemotherapy by cyclophosphamide, vincristine, and prednisone (CVP) alone. In former investigations, Hainsworth et al. [13] and Ghielmini et al. [14] already had found that R maintenance was beneficial when given to patients with FL who achieved a partial remission or complete remission after initial single-agent first-line R therapy. In a recent publication, R maintenance after R chemotherapy was investigated in patients with recurring or refractory FL and MCL. Patients were randomized to four courses of fludarabine, cyclophosphamide, and mitoxantrone (FCM) alone or combined with R (R-FCM). Response duration was significantly prolonged by R maintenance after R-FCM, with the median not being reached in this evaluation versus an estimated median of 16 months. This beneficial effect was also observed when analyzing FL and MCL separately [15]. However, the patient's quality of life (QoL) during rituximab maintenance therapy has not been analyzed systematically so far. In this analysis, we, for the first time, investigate the impact of rituximab maintenance therapy on the QoL in 91 patients with non-Hodgkin's lymphoma who were treated in a prospective randomized trial at our institution.

Materials and methods

Patients

In our institution, we performed a prospective randomized trial of rituximab maintenance therapy in patients with CD20+ B cell non-Hodgkin's lymphoma. After completion of standard treatment, patients were randomized to either observation or maintenance therapy with rituximab (375 mg/m^2) every 3 months for 2 years. Patients after first-line therapy as well as relapse patients were included in the study. Patients with aggressive lymphoma were enrolled if they had achieved a complete response after initial treatment. Patients with aggressive lymphoma with residual tumor mass were examined with positron emission tomography (PET) and qualified for randomization if PET showed no signs of tumor activity. Patients with indolent lymphoma qualified for the study if at least a partial response was achieved. The study was approved by the ethics committee of the University of Heidelberg, and an informed consent from all patients was obtained. The sponsors of the study were the University of Heidelberg and Roche, Basel, Switzerland. Rituximab was not provided by the corporate sponsor. The study has been registered at the ISRCTN (Trial number ISRCTN 74547745). A flow chart of the trial is shown in Fig. 1.

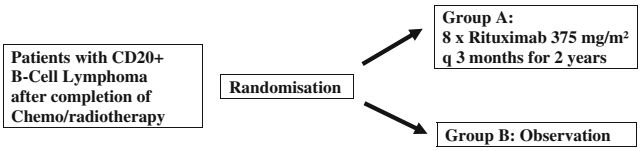

Fig. 1 Study design. Rituximab maintenance therapy in CD20+ B Cell Non-Hodgkin's lymphoma—concept of the prospective randomized trial

Table 1 Patient characteristics

	Group A treatment (n=47)	Group B observation (n=44)	Total (n=91)
Male gender (n, %)	29 (62%)	26 (59%)	55 (60%)
Age at randomisation in years, mean	55.19	56.53	54.59
Kind of previous therapy			
Conventional	29 (62%)	30 (68%)	59 (65%)
High dose with PBSCT	18 (38%)	14 (32%)	32 (35%)
Number of previous therapies (n, %)			
1	40 (85%)	32 (72%)	72 (79%)
2	6 (13%)	10 (23%)	16 (18%)
3	1 (3%)	1 (2%)	2 (2%)
Missing	0	1	1
Number of radiations			
0	30 (64%)	30 (68%)	60 (66%)
1	17 (36%)	12 (27%)	29 (32%)
2	0	1 (2%)	1 (1%)
3	0	1 (2%)	1 (1%)
Diagnosis (n)			
Diffuse large cell lymphoma	20	18	38
Mantle cell lymphoma	6	2	8
Follicular lymphoma	5	11	16
Primary mediastinal lymphoma	7	4	11
Marginal zone lymphoma	2	2	4
Burkitt lymphoma	2	1	3
Other	5	6	11

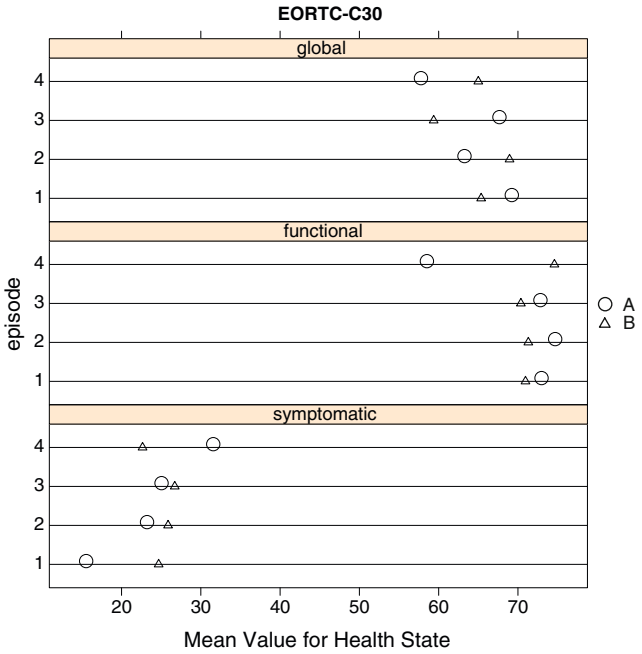

Fig. 2 EORT-C30: Mean values of QoL sum scores of treatment group (A, *circle*) and observation group (B, *triangle*) for each of the four treatment episodes and health state

Questionnaires

A set of questionnaires consisted of the EQ-5D and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (version 3.0). The EQ-5D is a generic instrument which measures five dimensions of health: mobility, self-care, daily activities, pain, and anxiety. In the descriptive part, the patient is required to rate his health on each of the five dimensions by checking one of the three levels of severity: no problems, some/moderate problems, or severe problems. The EQ-5D index assigns a preference value (utility) to each health state generated by the descriptive part of the questionnaire. The five-digit EQ-5D value of health state is then converted into an index value using the German time trade-off (TTO) value set [16]. The German TTO data value set ranges from −0.205 to 1, with a higher index value representing a better QoL. The EQ-5D visual analogue scales (VAS) instrument quantifies a self-rated description of the individual's overall health state on a scale of 0 (worst health state) to 100 (best health state).

The EORTC QLQ-C30 is a cancer-specific questionnaire which measures 30 single items. These items are added to three categories/scales: global health state/state of health, functional, and symptomatic state. After linear transformation according to EORTC scoring manual, all scales with their sum scores have numeric values between 0 and 100. A higher score of global health state and function scale implies a better QoL, whereas for symptomatic scale, a higher score refers to worse quality of life.

Statistical analysis

The impact of the rituximab maintenance therapy on the quality of life was analyzed using the EORTC QLQ-C30 and EQ-5D questionnaires. Patients were grouped into four treatment episodes according to the date of QoL investigation with respect to their individual treatment schedule. Patients who had received only 1 cycle rituximab at the

Table 2 Results of the EORTC-C30 questionnaire

	Mean group A	Standard deviation group A	Mean group B	Standard deviation group B	Estimated sum scores difference (group A minus group B)	95% CI	*p* values
Global state							
Episode1 (n=24)	68.75	17.25	65.36	14.57	4.17	(−12,5, 16,67)	0.57
Episode2 (n=26)	62.78	21.27	68.94	19.75	−8.33	(−25, 12.5)	0.43
Episode3 (n=28)	67.19	20.96	59.37	21.33	8.33	(−8.33, 25)	0.48
Episode4 (n=13)	57.29	30.68	65	25.28	−8.33	(−50, 33.33)	0.65
Functional state							
Episode1 (n=24)	72.5	26.82	70.95	14.87	6.67	(−22.22, 24.76)	0.62
Episode2 (n=26)	74.22	22.04	71.31	19.08	4.44	(−13.33, 22.22)	0.71
Episode3 (n=28)	72.36	23.49	70.37	21.32	2.22	(−17.78, 20)	0.71
Episode4 (n=13)	58.04	29.20	74.60	15.34	−13.17	(−44.44, 20)	0.34
Symptomatic state							
Episode1 (n=24)	15.06	15.53	24.68	15.27	−10.26	(−23.08, 2.56)	0.11
Episode2 (n=26)	22.74	15.13	25.87	17.71	−2.56	(−15.38, 10.26)	0.75
Episode3 (n=28)	24.57	20.29	26.71	19.01	−2.56	(−15.38, 10.26)	0.67
Episode4 (n=13)	31.09	25.18	22.65	11.51	7.69	(−20.51, 35.9)	0.72

time of the investigation were designated as 'episode 1' patients. Patients who had received 2 or 3 cycles rituximab were categorized in episode 2. Episode 3 consisted of patients who had received 4, 5, 6, or 7 cycles rituximab at the time of the investigation. Patients who had received all 8 cycles rituximab at the time of the investigation were designated as belonging to treatment episode 4.

The comparison of QoL scores between treatment and observation group was performed using the exact Wilcoxon rank sum test for each of the four treatment episodes. The Hodges–Lehmann estimates together with the corresponding 95% confidence interval for the differences of the distribution of sum scores between treatment and observation group (location parameter A–B) were computed. All results according to p values <0.05 were referred to as statistically significant. All statistical computations were done using R, version 2.5.1 [17], together with the R package 'coin', version 0.6–4.

Results

A one-time quality of life analysis was performed in January/February 2006 for those patients randomized to the trial until end of 2005. It was aimed to consider only patients without tumor relapse. Between July 2002 and December 2005, 122 patients were included into the trial. Until end of 2005, three patients were lost to follow-up or did not receive a therapy, 12 patients relapsed, one patient died in remission, and one patient was excluded because of a sepsis after osteomyelitis. One patient was incorrectly declared as a relapse, and one patient could not be identified. One hundred three patients received the questionnaires. Out of these 103 sets of questionnaires, 100 were sent back for evaluation. Two sets of questionnaires were sent back without name. Out of the 98, two were erroneously sent to relapsed patients and could therefore not be considered in further analyses. Treatment of four patients did not start at the time of investigation. For another patient, the date of the interview was lost. Therefore, these seven patients were additionally excluded from the analyses. Altogether, data from 91 patients were evaluable for the statistical analysis with respect to the set of questionnaires. There was an imbalance regarding the subtype of lymphoma between the treatment groups, with more patients with mantle cell lymphoma and primary mediastinal lymphoma in group A and more patients with follicular lymphoma in group B. Patient characteristics are shown in Table 1.

The EORTC QLQ-C30 is a cancer-specific questionnaire which measures 30 single items. These items are added to three categories/scales: global health state/state of health, functional, and symptomatic state. In this study, all categories were analyzed separately. No differences were found between the rituximab treatment group and the observation group for global health state, functional health state, and symptomatic health state. This was true as well for the total study population as well as for the four treatment episodes. Of note was a trend for worse

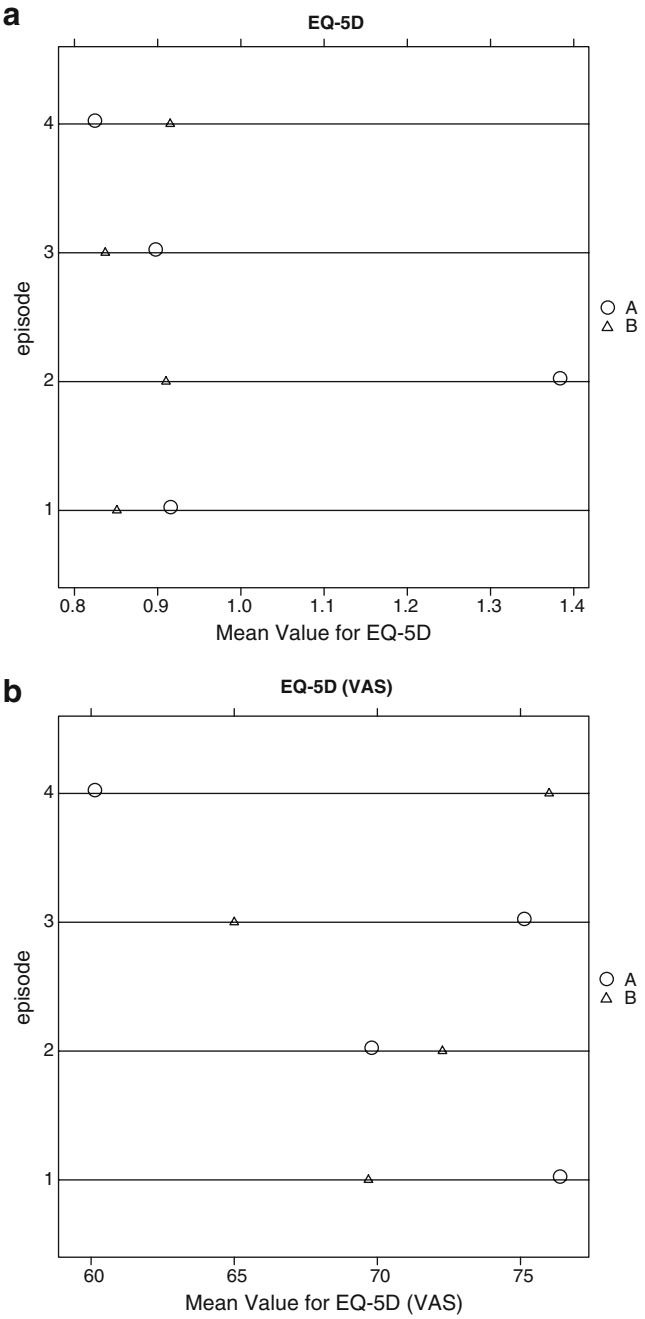

Fig. 3 **a** EQ-5D: Mean values of QoL sum scores of treatment group (A, *circle*) and observation group (B, *triangle*) for each of the four treatment episodes and EQ-5D questionnaire. **b** EQ-5D (VAS): Mean values of VAS score of treatment group (A, *circle*) and observation group (B, *triangle*) for each of the four treatment episodes and EQ-5D questionnaire

functional status and symptomatic status with increasing numbers of rituximab maintenance cycles. Figure 2 shows mean values for global, functional, and symptomatic health state for all four episodes. Table 2 additionally depicts standard deviation of the mean and the estimated sum score differences.

The questionnaire EQ-5D is a generic instrument which measures five dimensions of health: mobility, self-care, daily activities, pain, and anxiety. The EQ-5D VAS instrument quantifies a self-rated description of the individual's overall health state. Figure 3a shows the mean values for the EQ-5D and Fig. 3b the mean values for the EQ-5D (VAS) for all four treatment episodes. Table 3 depicts the standard deviation of the mean and the estimated sum score differences for the EQ-5D and for the EQ-5D (VAS) questionnaires. No statistically significant differences between the groups were found.

Discussion

The introduction of rituximab into the treatment of malignant lymphomas of the B cell lineage has had a major impact on the management of these diseases. Current studies have shown that a prolonged exposure to rituximab after the end of the primary treatment may reduce relapse rate and improve event-free survival in patients with FL and MCL [13–15]. In follicular lymphoma, rituximab maintenance therapy is now part of the standard of care in relapsed disease [10, 15]. In first-line therapy of follicular lymphoma, rituximab maintenance therapy has shown promising results in the trial of Hochster et al. [12] and is currently tested in two additional prospective randomized trials [18, 19]. In mantle cell lymphoma and diffuse large cell lymphoma, today, rituximab maintenance therapy is not part of the standard treatment but is tested in prospective randomized trials [11, 20].

For the individual patient, the effect of any antitumor therapy on the QoL is a very important question. In non-Hodgkin's lymphoma, only few studies examining the QoL in patients during treatment have been performed, and all these studies have been addressing patients treated in the pre-rituximab era [21–23].

There are, however, some studies in patients with autoimmune diseases in which quality of life was assessed during rituximab therapy. In a study with patients suffering from Sjogren's syndrome, QoL was investigated 6 months after beginning of rituximab therapy. There was a significant improvement from baseline in fatigue score, social functioning score, and in the mental health domain score in the rituximab group in contrast to the placebo group [24]. In patients with rheumatoid arthritis, the "International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial" could demonstrate an improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab [25]. However, these trials were performed with patients with active autoimmune disease, and the improvement of QoL is likely to be an effect of the direct action of rituximab in the pathogenesis of the disease symptoms. Hence, the results of these trials cannot be directly transferred to the situation of rituximab maintenance therapy in malignant lymphoma.

Therefore, so far, the question whether rituximab maintenance therapy may impair life quality in patients with non-Hodgkin's lymphoma has remained unanswered. To investigate on this subject, we have performed for the first time a systematic QoL analysis of a subset of patients of a prospective randomized trial of rituximab maintenance therapy (8 cycles rituximab 375 mg/m^2 every 3 months) versus observation in patients with CD20+ B cell non-Hodgkin's lymphoma. QoL was assessed with the standardized questionnaires EORTC-QLQ-C30, EQ-5D, and EQ-5D (VAS). The validity of any QoL study depends on the proportion of participating patients and the percentage

Table 3 SD of the mean and the estimated sum score differences for the EQ-5D and for the EQ-5D (VAS)

	Mean group A	Standard deviation group A	Mean group B	Standard deviation group B	Estimated sum scores difference (group A minus group B)	95% CI	*p* values
Results of the EQ-5D questionnaire							
Episode1 (n=24)	0.91	0.11	0.85	0.18	0.01	(−0.07, 0.11)	0.24
Episode2 (n=26)	1.38	2.13	0.91	0.08	0	(−0.1, 0.11)	0.82
Episode3 (n=28)	0.89	0.20	0.84	0.19	0.1	(0, 0.11)	0.09
Episode4 (n=13)	0.82	0.21	0.92	0.05	−0.01	(−0.38, 0.1)	0.54
Results of the EQ-5D (VAS) questionnaire							
Episode1 (n=24)	76.25	16.42	69.69	13.23	5	(−5, 20)	0.26
Episode2 (n=26)	69.67	18.66	72.27	18.62	−5	(−20, 15)	0.75
Episode3 (n=28)	75	20.74	65	17.58	10	(10, 0)	0.06
Episode4 (n=13)	60	26.05	76	14.75	−22.5	(−22.5, −40)	0.44

of returned questionnaires among participants. In this study, the participation was high, as 100 patients of the 103 patients who were asked to participate returned the questionnaires for evaluation. After statistical analysis of the EORTC-QLQ-C30 and EQ-5D questionnaires with the exact Wilcoxon rank sum test, we found no significant differences of the QoL scores between the rituximab treatment group and the observation group. Of note was a trend for worse functional status and symptomatic status with increasing numbers of rituximab maintenance cycles. One explanation for this effect could be the different relapse rates between the two groups. In group A (treatment group), only one patient had relapsed, whereas in group B (observation group), 11 relapses had been observed. Relapsed patients were excluded from the QoL analysis. These patients might have a reduced QoL before relapse, and by excluding these patients, the remaining patients particularly in group B could be biased towards a population with a better QoL profile. Taking our results together, we conclude that rituximab maintenance therapy seems to be safe and does not affect quality of life in this patient population.

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