

# Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group

Wolfgang Hiddemann, Michael Kneba, Martin Dreyling, Norbert Schmitz, Eva Lengfelder, Rudolf Schmits, Marcel Reiser, Bernd Metzner, Harriet Harder, Susanna Hegewisch-Becker, Thomas Fischer, Martin Kropff, Hans-Edgar Reis, Mathias Freund, Bernhard Wörmann, Roland Fuchs, Manfred Planker, Jörg Schimke, Hartmut Eimermacher, Lorenz Trümper, Ali Aldaoud, Reza Parwaresch, and Michael Unterhalt

**Phase 2 studies suggest that the monoclonal antibody rituximab may improve the prognosis of patients with follicular lymphoma (FL) when it is added to chemotherapy. In the current study, 428 patients with untreated, advanced-stage FL were randomly assigned for therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) alone (n = 205) or CHOP combined with rituximab (R-CHOP) (n = 223). R-CHOP reduced the relative risk for treatment failure by 60% and significantly prolonged the time to**

**treatment failure ( $P < .001$ ). In addition, a significantly higher overall response rate (96% vs 90%;  $P = .011$ ) and a prolonged duration of remission ( $P = .001$ ) were achieved. In spite of a relatively short observation time, these beneficial effects even translated to superior overall survival ( $P = .016$ ), with 6 deaths in the R-CHOP group compared with 17 deaths in the CHOP group within the first 3 years. The predominant treatment-related adverse effect was myelosuppression. Severe granulocytopenia was more**

**frequently observed after R-CHOP (63% vs 53%;  $P = .01$ ). However, severe infections were rare and of similar frequency after R-CHOP and CHOP (5% and 7%). Hence, adding rituximab to CHOP significantly improves the outcome for patients with previously untreated advanced-stage FL and does not induce major adverse effects. (Blood. 2005;106:3725-3732)**

© 2005 by The American Society of Hematology

## Introduction

Follicular lymphoma (FL) is the second most frequent lymphoma subtype worldwide.<sup>1</sup> Its incidence is rapidly increasing in Western countries and has nearly doubled within the past 3 decades. In most patients the disease is diagnosed at an advanced stage, III or IV, and cannot be cured by conventional therapeutic approaches. Hence, antilymphoma therapy is usually withheld for a watch-and-wait period until the disease becomes symptomatic. A broad spectrum of therapeutic options is available, ranging from radiotherapy to

single-agent to combination chemotherapy.<sup>2-4</sup> In spite of numerous efforts and the exploration of different treatment strategies, the prognosis of FL has literally remained unchanged in recent decades, with a median survival time of 8 to 10 years.<sup>5,6</sup>

Recently, new treatment modalities have been developed that justify the hope for improving the long-term outcome for patients with FL. These include myeloablative therapy followed by peripheral stem cell transplantation in younger patients, as indicated by a

From the Department of Internal Medicine III, University of Munich, Klinikum Großhadern; Department of Internal Medicine II, University Hospital Schleswig-Holstein, Campus Kiel; Department of Hematology and Oncology, Hospital St Georg, Hamburg; Department of Internal Medicine III, Klinikum Mannheim, University of Heidelberg; Department of Internal Medicine I, University of Homburg/Saar; Department of Internal Medicine I, University of Cologne; Department of Internal Medicine II, Oncology and Hematology, Klinikum Oldenburg; Department of Hematology, Oncology, and Tumor Immunology, Robert-Rössle-Klinik at the Helios Clinic Berlin-Buch, Charité, Campus Berlin-Buch; Department of Oncology, Klinikum Eppendorf, University of Hamburg; Department of Internal Medicine III, University of Mainz; Department of Internal Medicine A, University of Münster; Department of Hematology and Oncology, Kliniken Maria Hilf, Mönchengladbach; Department of Hematology and Oncology, University of Rostock; Department of Internal Medicine, Städtisches Klinikum Braunschweig; Department of Hematology and Oncology, St Antonius Hospital Eschweiler; Department of Hematology and Oncology, Städtische Krankenanstalten Krefeld; Praxis for Hematology and Oncology, Saarbrücken; Department of Hematology and Oncology, Katholisches Krankenhaus Hagen; Department of Hematology and Oncology, University of Göttingen; Praxis for Hematology and Oncology, Leipzig; and Department of Hemato-Pathology, University Hospital Schleswig-Holstein, Campus Kiel, Germany.

Submitted January 5, 2005; accepted May 25, 2005. Prepublished online as *Blood* First Edition Paper, August 25, 2005; DOI 10.1182/blood-2005-01-0016.

A complete list of the members of the German Low-Grade Lymphoma Study Group appears in participating "Appendix."

Supported by the Deutsche Krebshilfe (T14/96/Hi 1) and the Deutsches Bundesministerium für Bildung und Familie as part of the Competence Network Lymphomas.

W.H. wrote the manuscript; M. Kneba, M.D., N.S., T.F., M.F., B.W., L.T., R.P., and M.U. planned the study and wrote the study protocol; W.H., M. Kneba, M.D., N.S., E.L., R.S., M.R., B.M., H.H., S.H.-B., T.F., M. Kropff, H.-E.R., M.F., B.W., R.F., M.P., J.S., H.E., L.T., and A.A. treated patients and were responsible for documentation. R.P. organized the central pathology review. M.U. monitored the study, performed the statistical evaluation, and wrote the study report.

An Inside *Blood* analysis of this article appears in the front of this issue.

**Reprints:** W. Hiddemann, Department of Internal Medicine III, University of Munich, Großhadern Marchioninstr 15, 81377 München, Germany; e-mail: sekmed3@med.uni-muenchen.de.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 U.S.C. section 1734.

© 2005 by The American Society of Hematology

series of phase 2 studies.<sup>7-9</sup> Two recently completed prospective randomized phase 3 trials by the German Low-Grade Lymphoma Study Group (GLSG)<sup>10</sup> and the Groupe d'Études des Lymphomes de l'Adulte (GELA)<sup>11</sup> showed significant prolongation of the event-free interval and, in the GELA study, of overall survival after high-dose therapy with stem cell transplantation for patients with FL in complete remission (CR) or partial remission (PR) after initial cytoreductive chemotherapy. This approach is restricted, however, to younger patients and is hampered by the risk for secondary leukemias and myelodysplastic syndromes.<sup>12-15</sup> More specific, less toxic, and more broadly applicable treatment modalities are therefore warranted.

Monoclonal antibodies (mAbs) offer such a new and more targeted approach by serving as carriers for toxins or radioisotopes<sup>16-18</sup> or as direct cytotoxic agents with inherent antilymphoma activity. Among these different options, the chimeric human-mouse anti-CD20 mAb rituximab appears most promising. As shown by *in vitro* studies, rituximab is able to lyse CD20<sup>+</sup> cells by complement activation or antibody-dependent cell-mediated cytotoxicity.<sup>19</sup> Other potential mechanisms of action include the induction of apoptosis, blockage of the G<sub>1</sub>-S transition, impairment of differentiation, and increased phosphorylation of cellular proteins.<sup>20</sup> Because CD20 is expressed on many B-cell lymphomas, rituximab was expected to have a broad antilymphoma activity. Several phase 2 clinical trials, in fact, demonstrated a significant single-agent activity of rituximab in pretreated and in previously untreated patients with FL.<sup>21-25</sup> In follow-up studies, rituximab was combined with chemotherapy, which demonstrated not only high remission rates of more than 90% but, even more important, long-lasting periods of freedom from disease progression.<sup>26-28</sup>

The GLSG recently completed a prospective randomized trial of rituximab in combination with chemotherapy compared with chemotherapy alone in patients with relapsed or refractory FL and mantle cell lymphoma (MCL). This study demonstrated a significant benefit for the rituximab chemotherapy combination in terms of overall response, time to treatment failure (TTF), and, most important, overall survival.<sup>29</sup>

These highly encouraging data prompted the GLSG to embark on a prospective evaluation of a rituximab chemotherapy combination compared with chemotherapy alone in patients with previously untreated FL at advanced-stage disease. Based on encouraging phase 2 data as reported by Czuczman et al<sup>30</sup> and other investigators,<sup>31,32</sup> the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was chosen as the baseline regimen.

## Patients, materials, and methods

### Patients and entry criteria

This study was performed as a prospective, randomized, open-label multicenter phase 3 trial. It was started in 2000 and included patients 18 years of age and older with previously untreated, advanced-stage FL grades 1 and 2 according to the World Health Organization (WHO) classification.<sup>33</sup> Histologic diagnoses of all patients were to be confirmed by a central review at 1 of 6 designated pathology reference centers.

Clinical entry criteria were stage III or IV disease and a requirement for therapeutic intervention as defined by the presence of B-symptoms (night sweats, fever, or weight loss), bulky disease (mediastinal lymphomas greater than 7.5 cm or other lymphomas greater than 5 cm in maximal diameter), impairment of normal hematopoiesis with hemoglobin level less than 100 g/L, granulocyte count less than  $1.5 \times 10^9/L$ , thrombocyte count less than  $100 \times 10^9/L$ , or rapidly progressive disease. Patients were

ineligible if they had FL grade III, were pregnant or lactating, or were women of childbearing potential not using a reliable method of contraception.

The initial diagnostic work-up consisted of assessing the extent of the disease, including bone marrow biopsy, ultrasound examination of the abdomen, and computed tomography (CT) of the chest and abdomen. Normal organ function was confirmed by the respective laboratory tests and by echocardiography and electrocardiography.

### Randomization and treatment protocol

Before its initiation, the study was approved by the Institutional Review Board of the Department of Medicine, University of Munich, Germany. Patients were enrolled into the study by the responsible physician after having given their written informed consent. Each patient underwent a central randomization procedure at the study center. Randomization was performed by a computer program stratified for age and number of adverse prognostic factors, as defined by the International Prognostic Index (IPI)<sup>34</sup> using the method of random permuted blocks.

The CHOP combination consisted of cyclophosphamide 750 mg/m<sup>2</sup> administered intravenously on day 1, doxorubicin 50 mg/m<sup>2</sup> administered intravenously on day 1, vincristine 1.4 mg/m<sup>2</sup> (maximum, 2.0 mg) administered intravenously on day 1, and prednisone 100 mg/m<sup>2</sup> daily administered orally on days 1 to 5. Treatment cycles were repeated after every 3 weeks for a total of 6 to 8 cycles. Patients who were randomly assigned to the R-CHOP arm received a dose of rituximab 375 mg/m<sup>2</sup> the day before the respective R-CHOP course.

The number of cycles depended on the response to the first 4 courses. Patients achieving CR after 4 cycles were treated with a total of 6 cycles only, whereas all other patients received 8 courses of CHOP or R-CHOP. Patients with progressive disease at any time during CHOP or R-CHOP therapy were taken off study.

Patients younger than 60 years achieving CR or PR after CHOP or R-CHOP were offered a second randomization for treatment in remission to either intensification by the DexaBEAM regimen consisting of dexamethasone 3 × 8 mg/d orally on days 1 to 10, bischloroethylnitrosourea (BCNU) 60 mg/m<sup>2</sup> daily on day 2, melphalan 20 mg/m<sup>2</sup> daily intravenously on day 3, etoposide 75 mg/m<sup>2</sup> daily intravenously on days 4 to 7, and cytosine arabinoside 2 × 100 mg/m<sup>2</sup> every 12 hours intravenously on days 4 to 7 with subsequent stem cell harvest followed by myeloablative radiochemotherapy with total body irradiation (12 Gy) and cyclophosphamide 60 mg/kg daily for 2 days and stem cell retransfusion or long-term interferon- $\alpha$  (IFN- $\alpha$ ) maintenance initiated at a dose of 3 × 5 million U/wk and reduced according to observed adverse effects. IFN- $\alpha$  maintenance therapy was given until lymphoma progression or the development of intolerable adverse effects. The second randomization was stratified for the type of initial therapy (CHOP or R-CHOP) and the response to this treatment (CR or PR). All patients 60 years and older received IFN- $\alpha$  maintenance.

### Evaluation and response criteria

Response to therapy was assessed after every 2 cycles of CHOP or R-CHOP and 4 weeks after the completion of the last course. Response evaluation consisted of physical examination, determination of blood count and lactate dehydrogenase (LDH) level, ultrasound of the abdomen, and CT of previously involved areas. In patients otherwise fulfilling the criteria of CR, bone marrow biopsy was performed. Except for CT of previously involved areas, which was repeated every 6 months, these analyses were performed every 3 months as follow-up.

Response was defined according to the International Working Group criteria.<sup>35</sup> Hence, complete remission (CR) meant the elimination of all lymphoma manifestations for at least 4 weeks, including from the bone marrow, whereas partial remission (PR) was defined as a reduction of disease manifestations by at least 50% for more than 4 weeks. The category of unconfirmed complete remission (CRu) was not used. Instead, patients who fulfilled CR criteria but in whom bone marrow biopsy with evaluable negative result was not performed were considered to have achieved PR. The appearance of new nodal or extranodal manifestations or the enlargement of pre-existing lymphoma manifestations by more than 25% was considered disease progression.

TTF was defined as the interval between the start of treatment and the documentation of resistance to initial therapy, progressive disease, or death. Response duration was defined as the interval from the end of successful induction therapy to the documentation of progression or death, and overall survival was defined as the interval between the start of treatment and death.

Analyses were performed on an intention-to-treat basis without censoring for patients refusing the scheduled treatment in remission or receiving other unplanned therapies. Frequency and severity of adverse effects was recorded according to WHO toxicity criteria.

### Statistical analysis

The comparison of CHOP alone with R-CHOP was designed to test whether the addition of rituximab could reduce the risk for treatment failure by 50% according to a proportional hazards assumption.

On this basis, a one-sided triangular sequential test for log rank analysis with a working significance level of 0.01 was applied. This procedure allowed for the detection of the assumed superiority of R-CHOP over CHOP alone with a probability of 95%. The sequential procedure was designed to be equivalent in power and working significance level to a fixed sample test with 148 observations. After randomization was completed, further explorative analysis was performed of CR and overall remission rate, duration of response, time to next therapy, and overall survival using the Fisher exact test for binary responses and the log rank test and univariate Cox regression analysis for time-censored observations.

### Study conduct

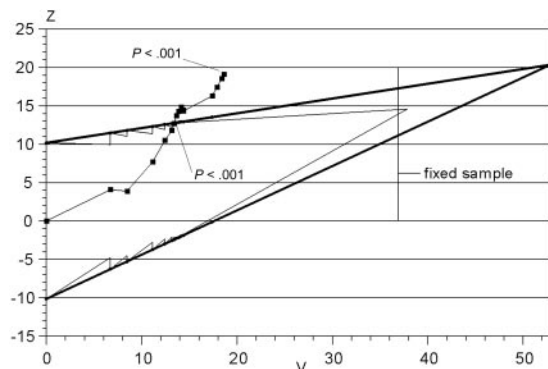
The study was carried out in accordance with the modified Declaration of Helsinki. All patients gave their written informed consent after having been informed about the purpose and investigational nature of the trial. Before initiation the study received approval by the responsible ethics committee.

## Results

Six hundred thirty patients with FL from 200 participating institutions of the GLSG were enrolled in the trial between May 2000 and August 2003. In June 2003 the applied one-sided sequential test showed a significantly longer TTF for the R-CHOP arm ( $P = .001$ ), and randomization was stopped according to the protocol in August 2003 (Figure 1).

### Patient characteristics

Only patients with completed documentation of initial therapy were evaluable for analysis. When randomization was stopped, 428 patients with FL were evaluable. The remaining 202 patients were



**Figure 1. Development of the one-sided sequential test of CHOP compared with R-CHOP over study time.** In June 2003, the sequential test reached the upper limit, indicating a significantly longer TTF after R-CHOP than after CHOP. Randomization was subsequently stopped.

**Table 1. Patient characteristics**

Characteristic	R-CHOP	CHOP
<b>Age</b>		
Median (range), y	54 (29-82)	57 (29-79)
60 and older, n (%)	82 (37)	85 (41)
<b>Sex, n (%)</b>		
Male	88 (39)	105 (49)
Female	135 (61)	100 (51)
<b>Extranodal involvement, %</b>		
Bone marrow	61	64
Liver	6	4
Spleen	33	40
Gastrointestinal tract	8	4
B-symptoms, %	36	43
<b>IPI score, %</b>		
1-2	81	80
3-5	19	20
LDH level elevated, %	23	23
More than 1 extranodal involvement, %	13	12
ECOG score greater than 1, %	7	9

Patient characteristics and risk factors are balanced between both study arms.

either still on initial cytoreduction therapy or had not yet been documented. Median age of the evaluable patients was 56 years (range, 29-82 years). One hundred sixty-seven (39%) patients were 60 years of age or older. All patients had advanced-stage disease (stage III or IV) and were in need of therapy before entering the study. In 390 patients the histologic diagnosis of follicular lymphoma grade 1 or 2 was confirmed by a central pathology review; in 38 patients, results are pending. Table 1 summarizes the main patient characteristics and indicates a balanced distribution between the 2 treatment arms.

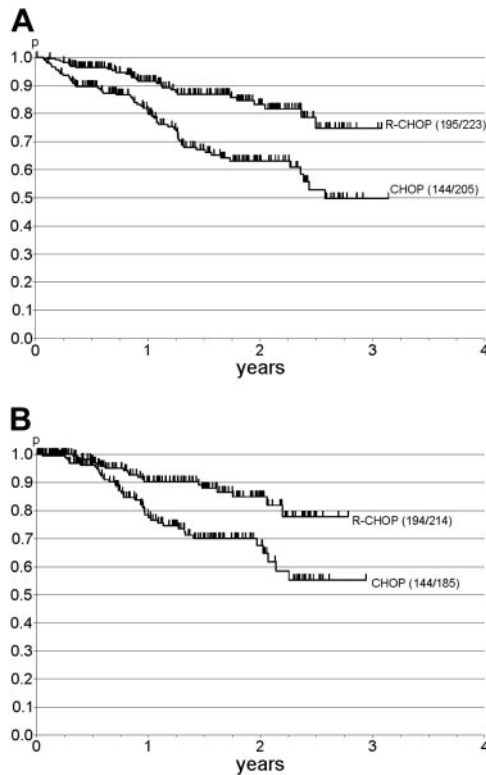
### Treatment results

Two hundred five patients were treated with CHOP alone, and 223 patients were treated with R-CHOP. Overall response rates were 96% with R-CHOP and 90% with CHOP alone ( $P = .011$ ); CR rates were not statistically different (20% vs 17%) (Table 2). After a median observation time of 18 months (range, 1-38 months), only 28 patients in the R-CHOP group experienced treatment failure compared with 61 patients in the CHOP group. Hence, R-CHOP led to a significant reduction in the risk for treatment failure by 60% and a significantly longer TTF ( $P < .001$ ) (Figure 2A). In addition, the rate of relapse or progression after successful initial therapy

**Table 2. Response rates for CHOP and R-CHOP**

	CHOP	R-CHOP
<b>Patients, n</b>		
Documented	205	223
Evaluable	205	222
<b>Remission</b>		
CR, n (%)	35 (17)	44 (20)
PR, n (%)	150 (73)	170 (77)
Overall response, CR + PR, n (%; 95% CI)	185 (90;85-94)	214 (96;93-98)
Minor response or stable disease, n (%)	11 (5)	4 (2)
Disease progression during therapy, n (%)	7 (3)	2 (1)
Death during therapy, n (%)	2 (1)	2 (1)

R-CHOP resulted in a significantly higher overall response rate (CR and PR) of 96% compared with 90% for CHOP ( $P = .011$ ); differences in the CR rate were not statistically significant. 95% CI indicates 95% confidence interval.



**Figure 2. Time to treatment failure and duration of response after CHOP and R-CHOP.** (A) TTF after start of therapy for CHOP and R-CHOP. In the R-CHOP arm, only 28 of 223 patients experienced treatment failure compared with 61 of 205 patients in the CHOP arm ( $P < .001$ ). (B) Duration of response after CHOP and R-CHOP. In patients achieving CR or PR after initial therapy, a significantly lower relapse rate was observed after R-CHOP than after CHOP ( $P = .001$ ).

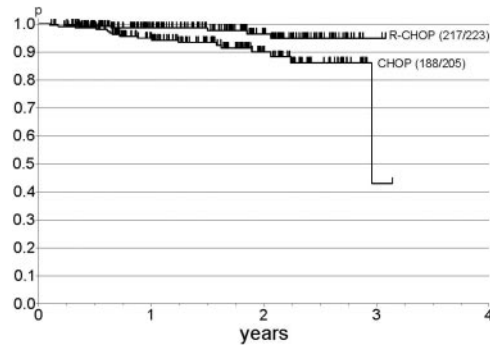
was significantly lower in R-CHOP–treated patients, resulting in a significantly longer duration of response ( $P = .001$ ) (Figure 2B). The outcome was favorable after R-CHOP therapy in all analyzed subgroups, including patients younger than 60 years and those 60 years and older and in patients with IPI scores of 1 or 2 compared with those of 3 to 5 (Table 3). Given that in FL disease progression does not necessarily require immediate retreatment, the time to next therapy was evaluated as well. For this parameter a significantly longer treatment-free interval was observed for R-CHOP–treated patients ( $P = .001$ ).

Although the observation period is still relatively short for an assessment of overall survival, an advantage for R-CHOP has been observed ( $P = .016$ ) (Figure 3). Hence, after 3 years, only 6

**Table 3. TTF for CHOP and R-CHOP based on patient age and IPI score**

Group	Estimated median TTF for CHOP	P for Cox regression	Estimated RR for treatment failure for R-CHOP	95% CI for RR
<b>Age, y</b>				
Younger than 60	Not reached	.003	0.417	0.233-0.747
60 and older	29 mo	.004	0.354	0.175-0.715
<b>IPI score</b>				
1-2	Not reached	.001	0.412	0.242-0.701
3-5	29 mo	.009	0.331	0.144-0.761

TTF was not reached in any category in this table for R-CHOP. R-CHOP therapy was significantly superior to CHOP therapy in younger and older patients and in patients with IPI scores of 1 or 2 and from 3 to 5. RR indicates relative risk; 95% CI, 95% confidence interval.



**Figure 3. OS after start of therapy for CHOP and R-CHOP.** Median OS has not been reached in either group. After 3 years, 6 patients in the R-CHOP arm have died compared with 17 patients in the CHOP arm ( $P = .016$ ).

patients assigned to R-CHOP therapy have died compared with 17 assigned to CHOP therapy (Table 4). The estimated probability of survival at 2 years is 95% for those treated with R-CHOP and 90% for those treated with CHOP.

**Adverse effects**

Treatment-associated hematologic adverse effects were predominantly myelosuppression, particularly granulocytopenia (Table 5). Grades 3 and 4 granulocytopenia occurred after 63% of R-CHOP cycles compared with 53% of CHOP cycles ( $P = .01$ ). This difference was clinically of minor relevance, however, because infections including fever of unknown origin were encountered after 5% of R-CHOP courses and after 7% of CHOP cycles only. Nonhematologic adverse events, which occurred at similar frequency after each regimen and were mostly mild to moderate, were primarily alopecia, nausea, and vomiting. Adverse events related to the infusion of rituximab were observed in 7% of courses during the first infusion; early cessation of rituximab therapy was required in 2 patients.

**Therapy in remission**

As indicated, patients younger than 60 years achieving CR or PR after R-CHOP or CHOP therapy were offered subsequent randomization for intensification followed by myeloablative radiochemotherapy and stem cell transplantation versus IFN- $\alpha$  maintenance. All elderly patients (60 years and older) received IFN- $\alpha$  maintenance therapy.

Of the 399 patients with CR or PR after initial therapy, 347 were evaluable for treatment strategies in remission. In 25 of these patients, no further treatment was applied (6% after R-CHOP and 8% after CHOP). Two hundred forty-three patients started IFN- $\alpha$  maintenance therapy (70% after R-CHOP and 70% after CHOP). Seventy-nine patients underwent intensification followed by myeloablative radiochemotherapy and stem cell transplantation (23% after R-CHOP and 22% after CHOP). These data show a balanced distribution of treatment in remission for the initial R-CHOP and CHOP arms, respectively.

At the time of this analysis, no differences were observed in patients after initial therapy with R-CHOP or CHOP who subsequently underwent intensification followed by myeloablative radiochemotherapy and stem cell transplantation. In patients receiving IFN- $\alpha$  maintenance therapy, however, a significantly longer duration of response has been observed for those who initially received R-CHOP treatment. Median duration of response has not yet been



**Table 4. Adverse effects after treatment with CHOP and R-CHOP**

Adverse effect	CHOP, %				R-CHOP, %			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin level	29	20	9	1	31	19	8	1
Leukocyte count	10	18	38	23	9	15	43	26
Granulocyte count	10	10	23	30	7	12	22	41
Platelet count	11	5	5	3	9	8	4	2
Bleeding	2	1	0	0	3	1	0	0
Nausea/vomiting	32	12	6	0	32	13	4	0
Stomatitis	23	6	2	0	18	8	1	0
Obstipation	10	3	1	0	9	6	2	0
Diarrhea	8	3	3	0	8	3	2	0
Fever	7	15	1	0	9	20	0	0
Alopecia	9	16	56	5	5	14	63	4
Infection	15	14	6	1	17	16	5	0
Cardiac dysfunction	2	2	1	0	2	1	2	1
Cardiac arrhythmia	2	2	0	0	5	1	1	1
Neurotoxicity	34	8	2	0	25	9	1	0
CNS toxicity	1	1	0	0	2	0	1	0
Allergy	0	0	0	0	3	3	1	0

Adverse effects were comparable between treatment arms with the exception of a higher frequency of severe granulocytopenia after treatment with R-CHOP ( $P = .01$ ). This difference was of clinically minor relevance, however, because no increase in infectious complications was observed.

reached for this group, whereas it was 26 months for patients receiving initial CHOP treatment ( $P < .001$ ) (Figure 4).

## Discussion

Results of the current study clearly show that the addition of rituximab to frontline therapy with CHOP leads to a significantly better outcome for patients with symptomatic, advanced-stage FL compared with those receiving CHOP alone. R-CHOP was superior to CHOP for all tested response parameters, including TTF ( $P < .001$ ), remission rate ( $P = .011$ ), response duration ( $P < .001$ ), time to next chemotherapy ( $P < .001$ ), and even overall survival (OS) ( $P = .016$ ). These beneficial effects were seen in all analyzed subgroups, including patients with low- or high-risk profiles according to the IPI or patients younger than 60 years and patients 60 years and older.

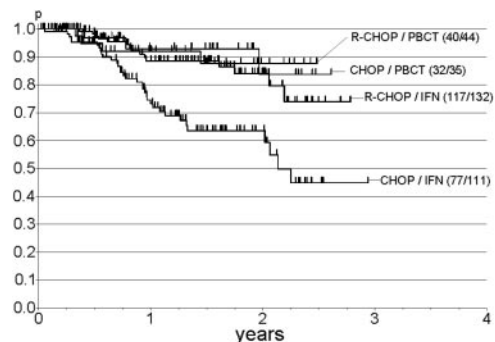
In a disease in which a curative approach is not yet available, the achievement of long periods without symptomatic disease and without the requirement of additional therapy is of great benefit to patients and is an essential goal of therapeutic measures aimed at a high quality of life. These goals can be achieved by R-CHOP in most patients without an increase of clinically relevant adverse effects. Although a high frequency (53%) of granulocytopenia grades 3 and 4 was observed after CHOP therapy and an even higher frequency (63%) was observed with R-CHOP therapy, this toxicity was clinically of moderate relevance since severe infec-

tions were only encountered after 5% of R-CHOP courses and after 7% of CHOP courses. It can certainly be argued that less intensive chemotherapeutic regimens, such as cyclophosphamide, vincristine, and prednisone (CVP) or even chlorambucil, induce fewer adverse effects. However, these therapies are associated with lower remission rates and shorter periods of progression-free survival requiring earlier and more frequent therapeutic interventions. The recently completed study by Marcus et al<sup>36</sup> investigated the addition of rituximab to CVP therapy compared with CVP therapy alone and showed a significant advantage for R-CVP for remission rate (81% vs 57%;  $P < .001$ ), TTF (27 months vs 7 months;  $P < .001$ ), and time to next therapy (median not reached vs 12 months;  $P < .001$ ). As in the current trial, this study demonstrates the beneficial effect of rituximab added to antilymphoma chemotherapy. However, remission rates and TTF achieved by R-CVP appear comparable to the results obtained by CHOP alone. A substantially better outcome seems to be achieved by R-CHOP. Adverse effects, particularly severe granulocytopenia, were less frequently encountered after CVP (14%) or R-CVP (24%) than after CHOP (53%) or R-CHOP (63%). However, clinically relevant

**Table 5. Causes of death after CHOP and R-CHOP therapy**

Cause	CHOP	R-CHOP
Progressive lymphoma	9	1
Infection	4	4
Cardiac failure	1	0
Apoplectic insult	1	0
GVHD after ASCT	1	0
Unknown	1	1

Six patients assigned to R-CHOP therapy died, compared with 17 patients assigned to CHOP therapy. GVHD indicates graft-versus-host disease; ASCT, allogeneic stem cell transplantation.



**Figure 4. Duration of response for patients receiving IFN- $\alpha$  maintenance therapy or undergoing peripheral blood stem cell transplantation after CHOP and R-CHOP.** Median duration of response has not been reached in patients receiving IFN- $\alpha$  maintenance after R-CHOP therapy, whereas it was 26 months after CHOP therapy ( $P = .001$ ). At the time of this analysis, no differences were observed in patients after initial therapy with R-CHOP or CHOP who subsequently underwent intensification therapy followed by myeloablative radiochemotherapy and peripheral blood stem cell transplantation (PBCT).

infections were rare in both studies, with 4% after CVP and R-CVP compared with 7% after CHOP and 5% after R-CHOP. Hence, the more intensive CHOP regimen might be a more effective and still well-tolerated basis for combination with rituximab.

A third recently completed randomized study by the GLSG investigated the addition of rituximab to a fludarabine, cyclophosphamide, and mitoxantrone (FCM) combination compared with FCM alone in patients with relapsed and refractory FL or mantle cell lymphoma. A significantly higher remission rate was also observed after R-FCM compared with FCM (79% vs 58%;  $P = .01$ ). In addition, the duration of remission was significantly prolonged (16 months vs 10 months;  $P = .038$ ) and, even more important, overall survival was significantly longer (median not reached vs 24 months;  $P = .003$ ).<sup>29</sup>

These studies consistently show that adding rituximab to chemotherapy is associated with an improved outcome in patients with advanced-stage FL. However, the type of regimen to which rituximab is added probably has an important impact on patient outcome and must be further defined by subsequent prospective randomized studies.

Two findings in the current trial suggest that R-CHOP may have long-lasting beneficial effects and may even lead to improvement in overall survival. Hence, in spite of a relatively short observation time and a low overall mortality rate, survival was significantly prolonged. After 3 years, only 6 patients on the R-CHOP arm have died compared with 17 patients treated with CHOP alone.

These data are further supported by the prolonged survival after R-FCM therapy of patients with relapsed FL or mantle cell lymphoma.<sup>29</sup> High proportions of patients with long-lasting disease-free and overall survival have also been observed by Czuczman et al<sup>28</sup> after R-CHOP therapy in a nonrandomized phase 2 study with a 9-year follow-up period.

The second indication for a potential long-lasting beneficial effect of R-CHOP arises from the finding that the duration of response of patients receiving IFN- $\alpha$  maintenance was significantly longer after R-CHOP therapy than it was after CHOP alone. These data strongly suggest that adding rituximab to the initial chemotherapy has a substantial influence on subsequent therapy during remission.

A recently completed study by the Eastern Cooperative Oncology Group (ECOG) showed 2.7-year longer PFS with 2 years of rituximab maintenance therapy after conventional cytoreductive therapy with CVP.<sup>37</sup> In 2 other studies rituximab was applied as initial single-agent therapy, and in this setting, the prolonged application proved superior to the "standard" schedule of  $4 \times 375$  mg/m<sup>2</sup>.<sup>38,39</sup>

The data from all these studies consistently show that rituximab has a significantly beneficial effect in patients with advanced-stage FL when given in addition to initial chemotherapy or when given as maintenance therapy after cytoreduction therapy without rituximab or as prolonged application single-agent therapy. Therefore, the question is no longer *whether* rituximab should be applied with first-line therapy for advanced-stage FL but *how* it should be applied. Although further studies are needed to address this question in greater detail, it may be speculated that these different ways of application might not be used alternatively but rather complementarily and that they might be appropriate for different patient populations as defined by age, performance status, IPI, or the recently introduced IPI for follicular lymphoma (FLIPI)<sup>40</sup> and other clinical or biologic risk factors. In this context, R-CHOP may be the preferred treatment option in patients with advanced-stage symptomatic disease in whom high remission rate and long-lasting remission are the primary goals of therapy.

## Appendix

The following participating institutions recruited patients into the study and are listed in descending order of numbers recruited (institutions are in Germany unless otherwise noted). The listed persons were responsible for the trial: R. Forstpointner, M. Dreyling, W. Hiddemann, Department of Internal Medicine III, Klinikum Großhadern, University of Munich; C. Pott, M. Kneba, Department of Internal Medicine II, Campus Kiel, University of Schleswig-Holstein; N. Schmitz, P. Dreger, Department of Hematology and Oncology, Allgemeines Krankenhaus St Georg, Hamburg; E. Lengfelder, C. Kuhn, R. Hehlmann, Department of Internal Medicine III, Klinikum Mannheim, University of Heidelberg; R. Schmits, M. Pfreundschuh, Department of Internal Medicine I, University of Homburg/Saar; B. Metzner, H. J. Illiger, Department of Internal Medicine II, Klinikum Oldenburg; M. Reiser, M. Hallek, Department of Internal Medicine I, University of Köln; H. Harder, W. D. Ludwig, Department of Hematology, Oncology, and Tumorimmunology, Helios Klinikum Berlin-Buch, Robert-Rössle-Klinik, Charité, Campus Berlin-Buch; S. Hegewisch-Becker, Department of Internal Medicine II, Klinikum Eppendorf, University of Hamburg; T. Fischer, G. Hess, C. Huber, Department of Internal Medicine III, University of Mainz; M. Kropff, R. Mesters, W. E. Berdel, Department of Internal Medicine A, University of Münster; D. Kohl, H.-E. Reis, Department of Hematology and Oncology, Kliniken Maria Hilf, Mönchengladbach; M. Freund, Department of Hematology and Oncology, University of Rostock; B. Wörmann, Department of Internal Medicine, Städtisches Klinikum Braunschweig; R. Fuchs, Department of Hematology and Oncology, St Antonius Hospital, Eschweiler; M. Planker, M. Busch, M. Hipp, Department of Internal Medicine II, Städtische Krankenanstalten, Krefeld; J. Schimke, G. Jacobs, H. Daus, Praxis of Hematology and Oncology, Saarbrücken; H. Eimermacher, Department of Hematology and Oncology, Katholisches Krankenhaus, Hagen; B. Glass, C. Binder, L. Trümper, Department of Hematology and Oncology, University of Göttingen; A. Aldaoud, A. Schwarzer, Praxis for Hematology and Oncology, Leipzig; J. Preiss, P. Schmidt, Department of Hematology and Oncology, Caritasklinik St Theresia, Saarbrücken; C. Spohn, Praxis of Hematology and Oncology, Halle/Saale; O. Burkhard, B. Reimann, Praxis of Internal Medicine and Hematology, Worms; M. Wiermann, Department of Hematology and Oncology, University of Magdeburg; L. Labedzki, H. J. Bias, Department of Internal Medicine, Kreiskrankenhaus Waldbröl; W. Aulitzky, S. Martin, Department of Hematology and Oncology, Robert-Bosch-Krankenhaus, Stuttgart; H.-G. Mergenthaler, J. Schleicher, Department of Hematology and Oncology, Katharinenhospital, Stuttgart; A. Neubauer, Department of Hematology, Oncology, and Immunology, University of Marburg; J. Mezger, G. Göckel, Department of Hematology and Oncology, St-Vincentius Krankenhäuser, Karlsruhe; E. D. Kreuser, Department of Hematology and Oncology, Krankenhaus Barmherzige Brüder, Regensburg; R. Veelken, J. Finke, R. Mertelsmann, Department of Hematology and Oncology, University of Freiburg; K. Höffken, H. J. Fricke, Clinic of Internal Medicine II, University of Jena; W. Fassbinder, H.-G. Höffkes, Department of Internal Medicine III, Klinikum Fulda; R. U. Steimann, Department of Internal Medicine, Krankenhaus Coesfeld; M. Stauch, Praxis of Hematology and Oncology, Kronach; H.-J. Hurtz, R. Rohrberg, R. Behrens, Praxis of Hematology and Oncology, Halle/Saale; H. Becker, Department of Internal Medicine I, Hans-Susemihl-Krankenhaus, Emden; H. P. Lohrmann, H. Middeke, Department of Internal Medicine II, Klinikum Lippe-Lemgo; C. Peschel, C. v. Schilling, Department of Hematology and Oncology, Klinikum Rechts der Isar, University of Munich; W. Gassmann, T. Gaska, Department of Internal Medicine III, St-Marien-Krankenhaus Siegen; M. Sandmann, G. Becker, Department of Hematology and Oncology, St Antonius Kliniken, Wuppertal; S. Siehl, U. Söling, Praxis of Hematology and Oncology, Kassel; S. Kraus, I. Hausbrandt, Department of Hematology and Oncology, St Salvator Krankenhaus, Halberstadt; W. W. Reiter, Praxis of Hematology and Oncology, Viersen; M. Baldus, Praxis of Hematology and Oncology, Rüsselsheim; S. Hollerbach,

Department of Gastroenterology, Allgemeines Krankenhaus Celle; P. Ketterer, O. Anders, Department of Oncology, Klinikum Südstadt, Rostock; H. Vetter, S. Fronhoffs, Department of Hematology and Oncology, Medizinische Poliklinik, University of Bonn; J. Pielken, V. Hagen, Department of Internal Medicine, St Johannes Krankenhaus, Dortmund; S. Fetscher, D. Nazareus, Department of Hematology and Oncology, Städtisches Krankenhaus Süd, Lübeck; W. Brugger, I. Funke, Department of Hematology and Oncology, Medizinische Klinik Villingen-Schwenningen; U. Schmitz-Huebner, Department of Internal Medicine II, Klinikum Kreis Herford; H. Wandt, J. Wortmann, Department of Hematology and Oncology, Klinik Nord und Medizinische Klinik, Nürnberg; U. Dührsens, H. Nüchel, Department of Hematology, Medizinische Klinik und Poliklinik, Essen; E. Heidemann, J. Kaesberger, Department of Internal Medicine II, Diakonissenkrankenhaus, Stuttgart; D. Unverferth, W. Langer, Department of Radiotherapy and Hematology, Kreiskrankenhaus Aurich; H. J. Weh, B. Angrick, Department of Internal Medicine II, Franziskus Hospital, Bielefeld; W. Augener, Department of Internal Medicine II, St-Willehad-Hospital, Wilhelmshaven; M. Gramatzki, Department of Internal Medicine III, University of Erlangen; A. A. Fauser, M. Kiehl, Klinik für Knochenmarkstransplantation, Hämatologie und Onkologie, Idar-Oberstein; U. Vehlring-Kaiser, Praxis of Hematology and Oncology, Landshut; H. Huff, Department of Internal Medicine II, Klinikum Rosenheim; V. Lakner, S. Decker, Praxis of Hematology and Oncology, Rostock; M. Schauer, Praxis of Hematology and Oncology, Nürnberg; J. Wehmeyer, C. Lerchenmüller, Praxis of Hematology and Oncology, Münster; G. Heil, D. Kämpfe, Department of Hematology and Oncology, Klinikum Lüdenscheid; J. Grunst, H. Lambertz, L. Schulz, Department of Internal Medicine I, Klinikum Garmisch-Partenkirchen; G. Schlimok, Department of Internal Medicine II, Zentralklinikum Augsburg; M. Wegener, E. Therhardt-Kasten, Department of Internal Medicine, Malteserkrankenhaus St Anna, Duisburg; K. Wilms, H. Rückle-Lanz, M. Wilhelm, Department of Internal Medicine, Medizinische Poliklinik, University of Würzburg; H. P. Böck, H. E. Ballo, Praxis of Hematology and Oncology, Offenbach; N. Peter, Department of Internal Medicine II, Carl-Thiem-Klinikum, Cottbus; P. Weber, Department of Oncology, Siloah Krankenhaus, Pforzheim; T. Reiber, D. Semsek, Praxis of Internal Medicine, Hematology and Oncology; Freiburg; M. Hahn, Praxis of Hematology and Oncology, Ansbach; J. T. Fischer, S. Wilhelm, R. Ehrhardt, Department of Hematology and Oncology, Städtisches Klinikum Karlsruhe; S. Kremers, H. Täger, Department of Hematology and Oncology, Caritas Krankenhaus, Lebach; R. Berger, Department of Internal Medicine, Knappschaftskrankenhaus, Dortmund; J. Diers, Department of Internal Medicine and Oncology, Marienhospital, Vechta; P. Hesse, Department of Internal Medicine, Asklepios Klinik Parchim; V. Gross, L. Fischer v. Weikersthal, Department of Internal Medicine II, Klinikum St Marien, Amberg; E. Kettner, G. Krötke, Department of Hematology and Oncology, Städtisches Klinikum, Magdeburg; M. Frickhofen, H.-G. Fuhr, G. Müller, Department of Internal Medicine III, Dr-H.-Schmidt-Kliniken Wiesbaden; F. W. Kleinsorge, Praxis of Internal Medicine, Hematology and Oncology, Detmold; M. R. Clemens, Department of Internal Medicine, Mutterhaus der Borromäerinnen, Trier; H. Keller, H. Leber, D. Nöcker, Department of Radio-oncology, Brüderkrankenhaus St Josef, Paderborn; C. Kölbl, W. Weber, H. Kirchen, Department of Internal Medicine I, Krankenhaus der Barmherzigen Brüder, Trier; A. Koschuth, D. Kingreen, Praxis of Internal Medicine, Hematology, and Oncology, Berlin; O. Prümmer, J. Gatter, Department of Internal Medicine III, Klinikum Kempten-Oberallgäu; F. Henne, Praxis of Hematology and Oncology, Hechingen; A. Hoyer, Department of Internal Medicine, Hematology and Oncology, Harzkliniken

Goslar; L. Mantovani, B. Matthé, Department of Hematology and Oncology, Städtisches Klinikum St Georg, Leipzig; K. Seitz, G. Käfer, Department of Internal Medicine and Oncology, Kreiskrankenhaus Sigmaringen; O. Brudler, B. Heinrich, Praxis of Hematology and Oncology, Augsburg; R. Hoffmann, Praxis of Hematology and Oncology, Norderstedt; W. Freier, Praxis of Oncology, Hildesheim; T. Bock, Praxis of Hematology and Oncology, Wittenberge; M. Grundheber, Praxis of Hematology and Oncology, Trier; M. Schwonzen, Department of Hematology and Oncology, St-Walburga-Krankenhaus, Meschede; A. Pfeiffer, Department of Internal Medicine II, Klinikum Memmingen; G. C. Schliesser, Praxis of Hematology, Giessen; U. von Grünhagen, Praxis of Hematology and Oncology, Cottbus; K. M. Josten, Praxis of Hematology and Oncology, Deutsche Klinik für Diagnostik, Wiesbaden; R. Voigtmann, E. Schilling, Department of Hematology and Oncology, Marienhospital Herne; R. Pasold, F. Rothmann, A. Haas, Department of Hematology and Oncology, Ernst-von-Bergmann-Klinik, Potsdam; T. Wagner, S. Peters, Department of Hematology and Oncology, University of Lübeck; I. Blau, Praxis of Hematology and Oncology, Berlin; S. Kruse, M. Don, Department of Internal Medicine, St Ansgar Krankenhaus, Hötter; U. M. Schmidt, J. Schneider, Praxis of Hematology and Oncology, Berlin; M. Schmelz, Department of Internal Medicine, Ermstal-Klinik, Bad Urach; G. Seipelt, Praxis of Hematology and Oncology, Bad Soden; U. Enserweis, Praxis of Hematology and Oncology, Bochum; C. zur Verth, Klinikum Itzehoe; D. Ellbrück, Praxis of Hematology, Memmingen; H. R. Schmitt, Praxis of Oncology, Gerlingen; R. Thoms, Praxis of Internal Medicine, Grefrath; N. Nikolaidis, Department of Internal Medicine, St Elisabeth Hospital, Beckum; H. Culmann, B. Höpner, Praxis of Internal Medicine, Hematology, and Oncology, Bergisch Gladbach; P. Schüssler, H. Tanzer, Department of Internal Medicine I, Städtisches Krankenhaus, Bad Reichenhall; M. Pauw, Department of Internal Medicine, Städtisches Krankenhaus Nettetal; H. G. Biedermann, Department of Internal Medicine, Kreisklinik Trostberg; R. Guggenberger, D. Tummes, R. Weinberg, Praxis of Internal Medicine, Hematology, and Oncology, Aachen; W. Maurer, Department of Internal Medicine and Oncology, Städtisches Krankenhaus, Neunkirchen; G. Schumann, M. Schunk, Department of Internal Medicine, Städtisches Krankenhaus Landau/Pfalz; M. Eckart, Praxis of Hematology and Oncology, Erlangen; A. Kehl, Department of Hematology and Oncology, Evangelisches Krankenhaus Wesel; U. Karbach, M. Schröder, Department of Internal Medicine, Hematology, and Oncology, Vinzentius-Krankenhaus Landau; H. Weiss, Department of Internal Medicine, St-Marien-Krankenhaus, Ludwigshafen; C. Maintz, Praxis of Hematology and Oncology, Würselen; M. Fromm, P. Borlinghaus, B. Sauter, Praxis of Hematology and Oncology, München; J. Brücher, B. Ullmann, Department of Internal Medicine, Robert-Koch-Krankenhaus, Geherden; E. Höring, M. v. Ehr, M. Respondek, Praxis of Hematology and Oncology, Stuttgart; E. Schäfer, M. Just, Praxis of Hematology and Oncology, Bielefeld; K. Verpoort, W. Zeller, Praxis of Hematology and Oncology, Hamburg; D. Fritze, A. Rost, Department of Internal Medicine V, Klinikum Darmstadt; S. Hahnfeld, B. Krombholz, Praxis of Internal Medicine, Hematology and Oncology, Jena; B. Rendenbach, Praxis of Oncology, Trier; H. Köppler, J. Heymanns, R. Weide, Praxis of Hematology and Oncology, Koblenz; K. H. Beckers, Department of Internal Medicine, St-Lukas-Klinik, Solingen-Ohligs; R. Paliege, P. B. Majunke, Department of Internal Medicine, Klinikum Bad Hersfeld; A. Knuth, J. Orth, Department of Internal Medicine II, Krankenhaus Nordwest, Frankfurt; W. Bootsvelde, Department of Internal Medicine, Hematology, and Oncology, Jakobi-Krankenhaus, Rheine; K. Günther, Klinik of Internal Medicine, Kreiskrankenhaus Reutlingen; and P. Czygan, Department of Internal Medicine II, Lukaskrankenhaus Neuss.

## References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma: the Non-Hodgkin's Lymphoma Classification Project. *Blood*. 1997;89:3909-3918.
2. Young RC, Longo DL, Glatstein E, Ihde DC, Jaffe ES, DeVita VT. The treatment of indolent lymphomas: watchful waiting vs aggressive combined modality treatment. *Semin Hematol*. 1988;25:11-16.
3. Solal-Céligny P, Lepage E, Brousse N, et al. Doxorubicin-containing regimen with or without interferon  $\alpha$ -2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 trial. *J Clin Oncol*. 1998;16:2332-2338.
4. Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the Cancer and Leukemia Group B. *J Clin Oncol*. 2003;21:5-15.
5. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med*. 1984;311:1471-1475.
6. Gallagher CJ, Gregory WM, Jones AE, et al. Follicular lymphoma: prognostic factors for response and survival. *J Clin Oncol*. 1986;4:1470-1480.
7. Freedman AS, Neuberger D, Mauch P, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. *Blood*. 1999;94:3325-3333.



8. Apostolidis J, Gupta RK, Grenzias D, et al. High-dose therapy with autologous bone marrow support as consolidation of remission in follicular lymphoma: long-term clinical and molecular follow-up. *J Clin Oncol*. 2000;18:527-536.
9. Horning SJ, Negrin RS, Hoppe RT, et al. High-dose therapy and autologous bone marrow transplantation for follicular lymphoma in first complete or partial remission: results of a phase II clinical trial. *Blood*. 2001;97:404-409.
10. Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group. *Blood*. 2004;104:2667-2674.
11. Sebban C, Blanger C, Brousse N, et al. Comparison of CHVP+interferon with CHOP followed by autologous stem cell transplantation with a TBI conditioning regimen in untreated patients with high tumor burden follicular lymphoma: results of the randomized GELF 94 trial (G.E.L.A. Study Group) [abstract]. *Blood*. 2003;102:104.
12. Micallef IN, Lillington DM, Apostolidis J, et al. Therapy-related myelodysplasia and secondary acute myelogenous leukemia after high-dose therapy with autologous hematopoietic progenitor-cell support for lymphoid malignancies. *J Clin Oncol*. 2000;18:947-955.
13. Park S, Brice P, Noguerra ME, et al. Myelodysplasia and leukemias after autologous stem cell transplantation for lymphoid malignancies. *Bone Marrow Transplant*. 2000;26:321-326.
14. Lenz G, Unterhalt M, Haferlach T, Hiddemann W, Dreyling M. Significant increase of secondary myelodysplasia and acute myeloid leukemia after myeloablative radiochemotherapy followed by autologous stem cell transplantation in indolent lymphoma patients: results of a prospective randomized study for the GLSG [abstract]. *Blood*. 2003;102:986.
15. Deconinck E, Foussard C, Bertrand PP, et al. Value of autologous stem cell transplantation in first line therapy of follicular lymphoma with high tumor burden: final results of the randomized GOELAMS 064 trial [abstract]. *Blood*. 2003;102:246.
16. Press OW, Eary JF, Gooley T, et al. A phase I/II trial of iodine-131-tositumomab (anti-CD20), etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsed B-cell lymphomas. *Blood*. 2000;96:2934-2942.
17. Kaminski MS, Estes J, Zasadny KR, et al. Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. *Blood*. 2000;96:1259-1266.
18. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:2453-2463.
19. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood*. 1994;83:435-445.
20. Shan D, Ledbetter JA, Press OW. Signaling events involved in anti-CD20-induced apoptosis of malignant human B cells. *Cancer Immunol Immunother*. 2000;48:673-683.
21. Maloney DG, Grillo-Lopez AJ, White CA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood*. 1997;90:2188-2195.
22. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16:2825-2833.
23. Feuring-Buske M, Kneba M, Unterhalt M, et al. IDEC-C2B8 (rituximab) anti-CD20 antibody treatment in relapsed advanced-stage follicular lymphomas: results of a phase-II study of the German Low-Grade Lymphoma Study Group. *Ann Hematol*. 2000;79:493-500.
24. Hainsworth JD, Litchy S, Burris HA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:4261-4267.
25. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. *Blood*. 2001;97:101-106.
26. Czuczman MS, Fallon A, Mohr A, et al. Rituximab in combination with CHOP or fludarabine in low-grade lymphoma. *Semin Oncol*. 2002;29(1 suppl 2):36-40.
27. Hiddemann W, Dreyling M, Unterhalt M. Rituximab plus chemotherapy in follicular and mantle cell lymphomas. *Semin Oncol*. 2003;30(suppl 2):16-20.
28. Czuczman MS, Weaver R, Alkuzweny B, Berfein J, Grillo-Lopez AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. *J Clin Oncol*. 2004;22:4659-4664.
29. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). *Blood*. 2004;104:3064-3071.
30. Czuczman MS, Grillo-Lopez AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Oncol*. 1999;17:268-276.
31. Maloney D, Press O, Brazier R. A phase II trial of CHOP followed by rituximab chimeric monoclonal anti-CD20 antibody for treatment of newly diagnosed follicular non-Hodgkin's lymphoma: SWOG 9800 [abstract]. *Blood*. 2001;98:843.
32. Rambaldi A, Lazzari M, Manzoni C, et al. Monitoring of minimal residual disease after CHOP and rituximab in previously untreated patients with follicular lymphoma. *Blood*. 2002;99:856-862.
33. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17:3835-3849.
34. Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329:987-994.
35. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. *J Clin Oncol*. 1999;17:1244-1253.
36. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105:1417-1423.
37. Hochster HS, Weller E, Ryan T, et al. Results of E 1496: a phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL) [abstract]. *Proc Am Soc Clin Oncol*. 2004;23:556.
38. Ghielmini M, Schmitz SF, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly  $\times 4$  schedule. *Blood*. 2004;103:4416-4423.
39. Hainsworth J, Litchy S, Greco FA. Scheduled rituximab maintenance therapy versus rituximab retreatment at progression in patients with indolent non-Hodgkin's lymphoma (NHL) responding to single-agent rituximab: a randomized trial of the Minnie Pearl Cancer Research Network [abstract]. *Blood*. 2003;102:69.
40. Solal Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104:1258-1265.





**blood**®

2005 106: 3725-3732

doi:10.1182/blood-2005-01-0016 originally published online  
August 25, 2005

**Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group**

Wolfgang Hiddemann, Michael Kneba, Martin Dreyling, Norbert Schmitz, Eva Lengfelder, Rudolf Schmits, Marcel Reiser, Bernd Metzner, Harriet Harder, Susanna Hegewisch-Becker, Thomas Fischer, Martin Kropff, Hans-Edgar Reis, Mathias Freund, Bernhard Wörmann, Roland Fuchs, Manfred Planker, Jörg Schimke, Hartmut Eimermacher, Lorenz Trümper, Ali Aldaoud, Reza Parwaresch and Michael Unterhalt

---

Updated information and services can be found at:

<http://www.bloodjournal.org/content/106/12/3725.full.html>

Articles on similar topics can be found in the following Blood collections

[Clinical Trials and Observations](#) (4630 articles)

[Free Research Articles](#) (4716 articles)

[Neoplasia](#) (4182 articles)

---

Information about reproducing this article in parts or in its entirety may be found online at:

[http://www.bloodjournal.org/site/misc/rights.xhtml#repub\\_requests](http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests)

Information about ordering reprints may be found online at:

<http://www.bloodjournal.org/site/misc/rights.xhtml#reprints>

Information about subscriptions and ASH membership may be found online at:

<http://www.bloodjournal.org/site/subscriptions/index.xhtml>