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

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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)

Introduction

Follicular lymphoma (FL) is the second most frequent lymphoma subtype worldwide.[1] 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.[2-4] 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.[5,6]

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

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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.

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series of phase 2 studies.[7-9] Two recently completed prospective randomized phase 3 trials by the German Low-Grade Lymphoma Study Group (GLSG)[10] and the Groupe d'Études des Lymphomes de l'Adulte (GELA)[11] 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.[12-15] 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[16-18] 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 $CD20^+$ cells by complement activation or antibody-dependent cell-mediated cytotoxicity.[19] Other potential mechanisms of action include the induction of apoptosis, blockage of the G_1-S transition, impairment of differentiation, and increased phosphorylation of cellular proteins.[20] 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.[21-25] 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.[26-28]

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.[29]

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[30] and other investigators,[31,32] 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.[33] 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 1.5×10^9/L, thrombocyte count less than 100×10^9/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)[34] using the method of random permutated blocks.

The CHOP combination consisted of cyclophosphamide 750 mg/m^2 administered intravenously on day 1, doxorubicin 50 mg/m^2 administered intravenously on day 1, vincristine 1.4 mg/m^2 (maximum, 2.0 mg) administered intravenously on day 1, and prednisone 100 mg/m^2 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^2 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^2 daily on day 2, melphalan 20 mg/m^2 daily intravenously on day 3, etoposide 75 mg/m^2 daily intravenously on days 4 to 7, and cytosine arabinoside 2×100 mg/m^2 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-α (IFN-α) maintenance initiated at a dose of 3×5 million U/wk and reduced according to observed adverse effects. IFN-α 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-α 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.[35] 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 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.

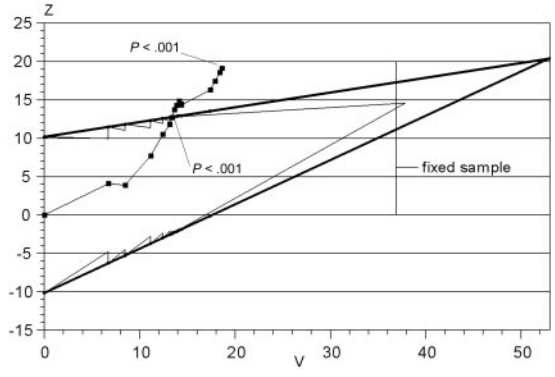

Figure 1. Development of the one-sided sequential test of CHOP compared with R-CHOP over study time. In June 2003, the sequential test reached the upper limit, indicating a significantly longer TTF after R-CHOP than after CHOP. Randomization was subsequently stopped.

Table 1. Patient characteristics

Characteristic	R-CHOP	CHOP
Age		
Median (range), y	54 (29-82)	57 (29-79)
60 and older, n (%)	82 (37)	85 (41)
Sex, n (%)		
Male	88 (39)	105 (49)
Female	135 (61)	100 (51)
Extranodal involvement, %		
Bone marrow	61	64
Liver	6	4
Spleen	33	40
Gastrointestinal tract	8	4
B-symptoms, %	36	43
IPI score, %		
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.

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
Patients, n		
Documented	205	223
Evaluable	205	222
Remission		
CR, n (%)	35 (17)	44 (2)
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.

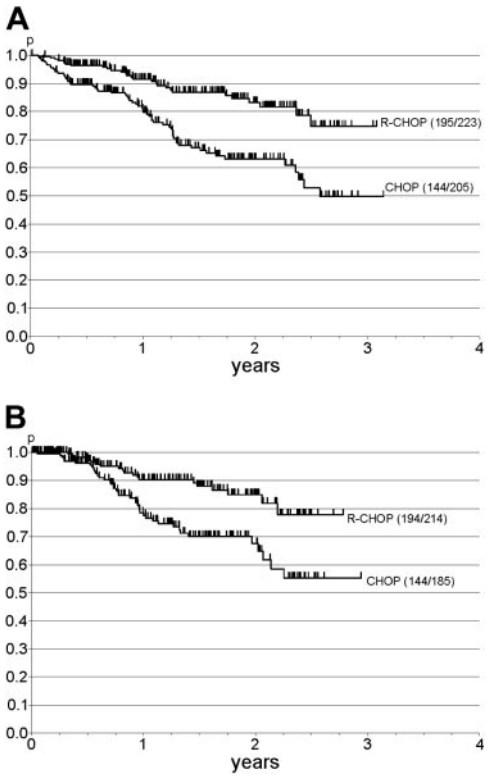

Figure 2. Time to treatment failure and duration of response after CHOP and R-CHOP. (A) TTF after start of therapy for CHOP and R-CHOP. In the R-CHOP arm, only 28 of 223 patients experienced treatment failure compared with 61 of 205 patients in the CHOP arm ($P < .001$). (B) Duration of response after 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
Age, y				
Younger than 60	Not reached	.003	0.417	0.233-0.747
60 and older	29 mo	.004	0.354	0.175-0.715
IPI score				
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.

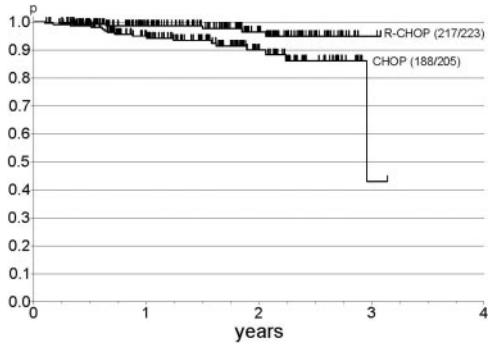

Figure 3. OS after start of therapy for CHOP and R-CHOP. Median OS has not been reached in either group. After 3 years, 6 patients in the R-CHOP arm have died compared with 17 patients in the CHOP arm ($P = .016$).

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-α maintenance. All elderly patients (60 years and older) received IFN-α 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-α 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-α 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

	CHOP, %				R-CHOP, %			
Adverse effect	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 infections 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[36] 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.

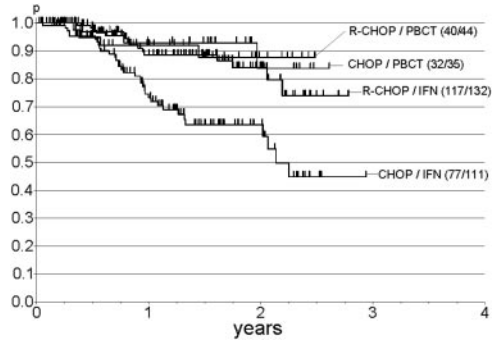

Figure 4. Duration of response for patients receiving IFN-α maintenance therapy or undergoing peripheral blood stem cell transplantation after CHOP and R-CHOP. Median duration of response has not been reached in patients receiving IFN-α maintenance after R-CHOP therapy, whereas it was 26 months after 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; $P = .003$).[29]

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.[29] High proportions of patients with long-lasting disease-free and overall survival have also been observed by Czuczman et al[28] 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-α 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.[37] 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 4×375 mg/m^2.[38,39]

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)[40] 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,

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