Front-Line Therapy with Rituximab added to the Combination of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) significantly improves the Outcome of Patients with Advanced Stage Follicular Lymphomas as compared to CHOP alone – Results of a Prospective Randomized Study of the German Low Grade Lymphoma Study Group (GLSG)


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ABSTRACT

Phase II studies suggest that the monoclonal antibody Rituximab (R) may improve the prognosis of patients with follicular lymphoma (FL) when added to chemotherapy. In the current study 428 patients with untreated advanced stage FL were randomized for therapy with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) alone (n=205) or combined with Rituximab (R-CHOP) (n=223). R-CHOP reduced the relative risk of treatment failure by 60% and prolonged the time to treatment failure significantly (p<0.0001). In addition, a significantly higher overall response rate (96% vs. 90%; p=0.011) and a prolonged duration of remission (p=0.0006) were achieved. In spite of a relatively short observation time these beneficial effects even translated into a superior overall survival (p=0.016) with six deaths in the R-CHOP group as compared to 17 deaths in the CHOP arm within the first three years. Treatment related side effects comprised predominantly myelosuppression. Severe granulocytopenia was more frequently observed after R-CHOP (63% versus 53%, p=0.01). However, severe infections were rare and of similar frequency after R-CHOP and CHOP (5% and 7%). Hence, the addition of Rituximab to CHOP significantly improves the outcome of patients with previously untreated advanced stage FL without adding major side effects.
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 last three decades. In the majority of patients the disease is diagnosed at an advanced stage III or IV and can not be cured by conventional therapeutic approaches. Hence, anti-lymphoma therapy is usually withheld for a watch and wait period until the disease becomes symptomatic. In this situation a broad spectrum of therapeutic options is available ranging from radiotherapy over 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 over the last decades with a median survival time of 8 – 10 years (5,6).

Recently, new treatment modalities have been developed which justify the hope for improving the long-term outcome of patients suffering from FL. These include myeloablative therapy followed by peripheral stem cell transplantation in younger patients as indicated by a series of phase II studies (7-9). Two recently completed prospective randomized phase III trials by the German Low Grade Lymphoma Study Group (GLSG) (10) and the Groupe D’Etudes des Lymphomes De l’Adulte (GELA) (11) showed a significant prolongation of the event free interval and in the GELA study also of overall survival after high dose therapy with stem cell transplantation when given to patients with FL in complete or partial remission after initial cytoreductive chemotherapy. This approach is restricted, however, to younger patients and is hampered by the risk of secondary leukemias and myelodysplastic syndromes (12-15). More specific, less toxic and more broadly applicable treatment modalities are therefore warranted. Monoclonal antibodies (mAB) offer such a new and more targeted approach by serving as carriers for toxins or radioisotopes (16-18) or as direct cytotoxic agents with an 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.
Other potential mechanisms of action include the induction of apoptosis, a block of the G1/S-transition, an impairment of differentiation and an increased phosphorylation of cellular proteins. Since CD20 is expressed on many B cell lymphomas Rituximab was expected to have a broad antilymphoma activity. Several phase II clinical trials in fact demonstrated a significant single agent activity of Rituximab in pretreated as well as in previously untreated patients with FL. In follow-up studies Rituximab was combined with chemotherapy which demonstrated not only high remission rates of more than 90% but even more importantly long lasting periods of freedom from disease progression.

The GLSG recently completed a prospective randomized trial of Rituximab in combination with chemotherapy versus chemotherapy alone in patients with relapsed or refractory FL and mantle cell lymphomas (MCL). This study demonstrated a significant benefit for the R-chemotherapy combination in terms of overall response, time to treatment failure and most importantly overall survival.

These highly encouraging data prompted the GLSG to embark on a prospective evaluation of a Rituximab chemotherapy combination versus chemotherapy alone in patients with previously untreated FL at advanced stage disease. Based on encouraging phase II data as reported by Czuczman et al. and other investigators the combination of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) was chosen as baseline regimen.

**PATIENTS, TREATMENT PROTOCOL AND METHODS**

**Patients and Entry Criteria**

This study was performed as a prospective, randomized, open-label multicenter phase III trial. It was started in 2000 and included patients of ages 18 years and older with previously untreated advanced stage follicular lymphomas grades I and II according to the WHO
classification (33). The histologic diagnosis of all patients were to be confirmed by a central review at one of six designated pathology reference centers.

Clinical entry criteria comprised stage III or IV disease and a requirement for therapeutic intervention as defined by the presence of B-symptoms and/or bulky disease (mediastinal lymphomas >7.5 cm or other lymphomas >5 cm in maximal diameter) and/or an impairment of normal hematopoiesis with hemoglobin <10 g/mm$^3$ and/or granulocytes <1500/mm$^3$ and/or thrombocytes <100,000/mm$^3$ and/or a rapidly progressive disorder.

Patients with follicular lymphomas of grade III were not eligible, neither were pregnant nor lactating women nor women of childbearing potential not using a reliable contraceptive method.

The initial diagnostic work-up comprised the assessment of the extent of the disease including bone marrow biopsy, ultrasound examination of the abdomen and CT scans of chest and abdomen. Normal organ function was assured by the respective laboratory tests, as well as by echo- and electrocardiograms.

**Randomization and Treatment Protocol**

Prior to 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. All patients underwent a central randomization procedure at the study center. Randomization was done by a computer program stratified for age and the number of adverse prognostic factors as defined by the International Prognostic Index (IPI) (34) using the method of random permuted blocks.

The CHOP combination comprised Cyclophosphamide 750 mg/m$^2$/d i.v. on day 1, Doxorubicin 50 mg/m$^2$/d i.v. on day 1, Vincristine 1.4 mg/m$^2$/d (max. 2.0 mg/d) i.v. on day 1 and Prednisone 100mg/ m$^2$/d orally on days 1 - 5. Treatment cycles were repeated after every
three weeks for a total of six to eight cycles. Patients who were randomized into the R-CHOP arm received a dose of 375 mg/m²/d Rituximab on the day before the respective R-CHOP course.

The number of cycles depended on the response to the first four courses. Patients achieving a complete remission after four cycles already were treated with a total of six cycles only while all other cases received eight CHOP or R-CHOP courses, respectively. Patients with progressive disease at any time during CHOP or R-CHOP therapy were taken off study.

Patients < 60 years achieving a complete or partial remission after CHOP or R-CHOP were offered a second randomization for treatment in remission to either intensification by the DexaBEAM regimen comprising Dexamethason 3 x 8 mg orally on days 1 – 10, BCNU 60 mg/m²/d on day 2, Melphalan 20 mg/m²/d i.v. on day 3, Etoposide 75 mg/m²/d i.v. on days 4 – 7 and Cytosine Arabinoside 2 x 100 mg/m²/q 12 hrs. i.v. on days 4 – 7 with subsequent stem cell harvest followed by myeloablative radiochemotherapy with total body irradiation (12 Gy) and Cyclophosphamide 60 mg/kg/d for two days and stem cell retransfusion or long term Interferon alpha maintenance was initiated at a dose of 3 x 5 Mill. Units/week and was reduced according to observed side effects. Interferon alpha maintenance therapy was given until lymphoma progression or the development of intolerable side 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 of age received Interferon alpha maintenance.

**Evaluation and Response Criteria**

Response to therapy was assessed after every two cycles of CHOP or R-CHOP, respectively and 4 weeks after the completion of last course. Response evaluation comprised a physical examination, the determination of blood counts and LDH, an ultrasound of the abdomen and
CT scans of previously involved areas. In patients fulfilling otherwise the criteria of a complete remission a bone marrow biopsy was performed.

For follow-up the aforementioned analyses were performed every three months except for CT scans of previously involved areas, which were repeated every six months.

Response was defined according to the International Working Group criteria (35). Hence, complete remission (CR) comprised the elimination of all lymphoma manifestations for at least 4 weeks including the bone marrow, while partial remission (PR) was defined as a reduction of disease manifestations by at least 50% for more than 4 weeks. In modification of the afore mentioned criteria, the category of unconfirmed complete remission (CRu) was not used. Instead, patients who fulfilled CR criteria but in whom no bone marrow biopsy with evaluable negative result was performed were counted as PR. The appearance of new nodal or extranodal manifestations or the enlargement of preexisting lymphoma manifestations by more than 25% were considered as progression.

Time to treatment failure 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 documentation of progression or death, and overall survival as the interval between the start of treatment to 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.

The frequency and severity of side effects was recorded according to WHO toxicity criteria.

**Statistics**

The comparison of CHOP alone vs. R-CHOP was designed to test whether the addition of Rituximab could reduce the risk for treatment failure by 50% according to a proportional hazard assumption.
On this basis a one-sided triangular sequential test for the logrank analysis with a working significance level of 0.01 was applied. This procedure allowed to detect 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 the end of randomization a further explorative analysis was done for the complete and overall remission rate, the duration of response, the time to next therapy and the overall survival using the Fisher-test for binary responses and the logrank-test and univariate Cox-regression for time-censored observations.

**Study Conduct**

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

**RESULTS**

Six hundred and thirty patients with follicular lymphomas from 200 participating institutions of the GLSG were enrolled into the trial between May 2000 and August 2003. In June 2003 the applied one sided sequential test showed a significantly longer time to treatment failure for the R-CHOP arm (p=0.000615) and randomization was stopped according to the protocol in August 2003 (Fig. 1).

**Patients Characteristics**

Only patients with completed documentation of initial therapy were evaluable for this analysis. At the time point when randomization was stopped a total of 428 patients with follicular lymphoma were evaluable. The remaining 202 patients were either still on initial
cytoreductive therapy or had not been documented yet. The median age of the evaluable patients was 56 years, with a range from 29 to 82 years. One hundred and sixty seven cases (39%) were 60 years of age or older. All patients had advanced stage disease of stages III or IV and were in need of therapy before entering the study. In 390 patients the histologic diagnosis of follicular lymphoma grade I or II was confirmed by a central pathologic review, in 38 patients results are pending. Table 1 summarizes the main patient characteristics and indicates a balanced distribution between the two treatment arms.

Figure 1: Development of the one sided sequential test of CHOP versus R-CHOP over study time

In June 2003 the sequential test hit the upper limit indicating a significantly longer time to treatment failure after R-CHOP versus CHOP and randomization was subsequently stopped.
### Table 1: Patient Characteristics

Patient characteristics and risk factors are balanced between both study arms

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (years)/ Range</td>
<td>54 (29 - 82)</td>
<td>57 (29 - 79)</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>82 (37%)</td>
<td>85 (41%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>88 (39%)</td>
<td>105 (49%)</td>
</tr>
<tr>
<td>Female</td>
<td>135 (61%)</td>
<td>100 (51%)</td>
</tr>
<tr>
<td><strong>Extra Nodal Involvement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>61 %</td>
<td>64 %</td>
</tr>
<tr>
<td>Liver</td>
<td>6 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Spleen</td>
<td>33 %</td>
<td>40 %</td>
</tr>
<tr>
<td>GI tract</td>
<td>8 %</td>
<td>4 %</td>
</tr>
<tr>
<td><strong>B-symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 %</td>
<td>43 %</td>
</tr>
<tr>
<td><strong>IPI score 1 - 2:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81 %</td>
<td>80 %</td>
</tr>
<tr>
<td><strong>IPI score 3 - 5:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 %</td>
<td>20 %</td>
</tr>
<tr>
<td><strong>LDH elevated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 %</td>
<td>23 %</td>
</tr>
<tr>
<td>&gt; 1 extranodal involvements</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 %</td>
<td>12 %</td>
</tr>
<tr>
<td><strong>ECOG &gt; 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 %</td>
<td>9 %</td>
</tr>
</tbody>
</table>
Treatment Results

Two hundred and five patients were treated with CHOP alone, 223 cases received the R-CHOP regimen. In the R-CHOP arm a significantly higher overall response rate of 96% versus 90% for CHOP alone was observed (p = 0.011) while the CR rates were not statistically different (20% versus 17%) (Table 2).

Table 2: Response rates for CHOP and R-CHOP

R-CHOP revealed a significantly higher overall response (CR and PR) of 96% versus 90% for CHOP (p=0.011) while the differences in the CR rate were not statistically significant.

<table>
<thead>
<tr>
<th></th>
<th>CHOP</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented patients:</td>
<td>205</td>
<td>223</td>
</tr>
<tr>
<td>Evaluable:</td>
<td>205</td>
<td>222</td>
</tr>
<tr>
<td>Complete Remission:</td>
<td>35 17%</td>
<td>44 20%</td>
</tr>
<tr>
<td>Partial Remission:</td>
<td>150 73%</td>
<td>170 77%</td>
</tr>
<tr>
<td>Minor Response or Stable Disease:</td>
<td>11 5%</td>
<td>4 2%</td>
</tr>
<tr>
<td>Progression during Therapy:</td>
<td>7 3%</td>
<td>2 1%</td>
</tr>
<tr>
<td>Death during Therapy:</td>
<td>2 1%</td>
<td>2 1%</td>
</tr>
<tr>
<td>Overall Response (CR+ PR):</td>
<td>185 90% (85 - 94)</td>
<td>214 96% (93 - 98)</td>
</tr>
</tbody>
</table>

After a median observation time of 18 months (range 1 – 38 months) only 28 patients on the R-CHOP arm experienced a treatment failure as compared to 61 cases treated with CHOP.
alone. Hence, R-CHOP lead to a significant reduction of the risk of treatment failure by 60% and a significantly longer the time to treatment failure (p<0.0001) (Figure 2a). In addition, the rate of relapse or progression after successful initial therapy was significantly lower in R-CHOP treated patients resulting in a significantly longer duration of response (p=0.0006) (Figure 2b). The favorable outcome after R-CHOP was present in all analyzed subgroups including patients younger or older than 60 years or cases with IPI scores 1-2 versus 3-5 (Table 3). Since in follicular lymphomas progression does not necessarily require immediate retreatment, the time to next therapy was evaluated as well. Also for this parameter a significantly longer treatment free interval was observed for R-CHOP treated patients (p=0.0009).

Figure 2a: Time to treatment failure after start of therapy for CHOP or R-CHOP

In the R-CHOP arm only 28 of 223 patients experienced a treatment failure as compared to 61 of 205 cases in the CHOP alone group (p<0.0001).
Figure 2b: Duration of response after CHOP or R-CHOP

In patients achieving a complete or partial remission after initial therapy a significantly lower relapse rate was observed in the R-CHOP arm as compared to CHOP alone (p = 0.0006).
Table 3: Time to treatment failure for CHOP and R-CHOP for patients < years and > 60 years of age and for patients with IPI scores 0-2 and 3-5.

R-CHOP was significantly superior to CHOP in younger and older patients as well as in patients with IPI 0-2 or 3-5. IPI = International Prognostic Index

<table>
<thead>
<tr>
<th>Group</th>
<th>estimated median time to treatment failure for CHOP/ R-CHOP</th>
<th>sign. for Cox-Regr.</th>
<th>estimated relative risk of treatment failure for R-CHOP</th>
<th>95%-confidence intervals for relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>age &lt; 60 years</td>
<td>not reached in both arms</td>
<td>0.003</td>
<td>0.417</td>
<td>0.233 - 0.747</td>
</tr>
<tr>
<td>age &gt; 60 years</td>
<td>29 months for CHOP / not reached in R-CHOP</td>
<td>0.004</td>
<td>0.354</td>
<td>0.175 - 0.715</td>
</tr>
<tr>
<td>IPI score 1-2</td>
<td>not reached in both arms</td>
<td>0.001</td>
<td>0.412</td>
<td>0.242 - 0.701</td>
</tr>
<tr>
<td>IPI score 3-5</td>
<td>29 months for CHOP / not reached in R-CHOP</td>
<td>0.009</td>
<td>0.331</td>
<td>0.144 - 0.761</td>
</tr>
</tbody>
</table>

At this time the observation period is still relatively short for an assessment of overall survival. Still, an advantage for R-CHOP is currently observed (p=0.016)(Figure 3). Hence, after three years only six patients assigned to R-CHOP therapy have died as compared to 17 cases that were treated with CHOP (Table 4). The estimated probability of survival at two years is 95% for R-CHOP and 90% for CHOP.
Table 4: Causes of death for CHOP and R-CHOP

Six patients assigned to R-CHOP therapy have died as compared to 17 cases that were treated with CHOP.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>CHOP</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death after start of therapy:</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Progressive lymphoma:</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Infection:</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac failure:</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Apoplectic insult:</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Graft vs. host disease after allogeneic SCT</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Unknown cause of death:</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
The median OS is not reached in both groups. After three years six patients on the R-CHOP arm have died as compared to 17 cases on the CHOP arm (p=0.016).

**Side effects**

Treatment associated side hematologic effects comprised predominantly myelosuppression and granulocytopenia in particular (Table 5). Granulocytopenia of grade 3 and 4 occurred after 63% of R-CHOP cycles as compared to 53% of CHOP courses (p=0.01). This difference was clinically of minor relevance, however, since infections including fever of unknown origin were encountered after 5% of R-CHOP courses and after 7% of CHOP cycles, only. Non-hematologic side effects consisted mainly of alopecia, nausea and vomiting, which occurred at similar frequencies after both regimens and were mostly mild to moderate. Adverse events related to the infusion of Rituximab were observed in 7% of courses during the first infusion, an early cessation of Rituximab therapy was required in two patients.
Table 5: Side effects after treatment with CHOP and R-CHOP.

Side effects were comparable between both treatment arms with the exception of a higher frequency of severe granulocytopenia after treatment with R-CHOP (p=0.01). This difference was clinically of minor relevance, however, since no increase in infectious complications was observed.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>CHOP</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>grade 1</td>
<td>grade 2</td>
</tr>
<tr>
<td>HB</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Platelets</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Obstipation</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Infection</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Cardiac dysf.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac rythm.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>CNS-Toxicity</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Allergy</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Therapy in remission

As indicated above, patients < 60 years of age achieving a CR or PR after R-CHOP or CHOP therapy were offered a subsequent randomization for intensification followed by myeloablative radiochemotherapy and stem cell transplantation versus Interferon alpha maintenance. All elderly patients received Interferon alpha maintenance.

Of the 399 patients with CR or PR after initial therapy 347 were evaluable for treatment strategies in remission. In 25 of these cases no further treatment was applied (6% after R-CHOP and 8% after CHOP). Two hundred and forty-three patients started Interferon alpha maintenance (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 are 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 Interferon alpha maintenance, however, a significantly longer duration of response was observed after R-CHOP therapy. In this group of patients the median duration is not yet reached whereas it is 26 months after initial CHOP treatment (p=0.0004) (Figure 4).

DISCUSSION

The results of the current study clearly show that the addition of Rituximab (R) to front line therapy with Cyclophosphamide, Vincristine, Doxorubicin and Prednisone (CHOP) leads to a significantly better outcome of patients with symptomatic, advanced stage follicular lymphoma as compared to CHOP alone. R-CHOP was superior to CHOP for all tested response parameters including time to treatment failure (TTF) (p<0.0001), remission rate (p=0.011), response duration (p=0.0006), time to next chemotherapy (p=0.0009) and even overall
survival (OS) \( (p=0.016) \). These beneficial effects were seen in all analyzed subgroups including patients with a low or high-risk profile according to the international prognostic index (IPI) or patients younger and older than 60 years of age.

**Figure 4:** Duration of response for patients receiving Interferon alpha maintenance or PBCT after CHOP or R-CHOP.

![Duration of response for patients receiving Interferon alpha maintenance or PBCT after CHOP or R-CHOP.](image)

In patients receiving Interferon alpha maintenance after R-CHOP the median duration of response is not reached whereas it is 26 months after CHOP \( (p=0.0004) \). At the time of this analysis no differences are observed in patients after initial therapy with R-CHOP or CHOP who subsequently underwent intensification followed by myeloablative radiochemotherapy and stem cell transplantation (PBCT).

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 comprises an essential goal of therapeutic measures aiming at a high quality of life. These goals can be achieved by R-CHOP in the vast majority of patients without an increase of clinically relevant side effects. Although a high frequency of granulocytopenia grades 3 and 4 was observed after CHOP alone already (53%) that was even higher with R-CHOP (63%), this toxicity was clinically of moderate relevance since severe infections were encountered after 5% of R-CHOP courses and after 7% of CHOP cycles, only. It can certainly be argued that less intensive chemotherapeutic regimens such as Cyclophosphamide, Vincristine, Prednisone (CVP) or even Chlorambucil have fewer side 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 versus CVP alone and showed a significant advantage for R-CVP for remission rate (81% versus 57%, p<0.0001) and TTF (27 months versus 7 months, p<0.0001) as well as for time to next therapy (median not reached versus 12 months, p<0.0001). Like the current trial this study demonstrates the beneficial effect of Rituximab added to antilymphoma chemotherapy. However, remission rates and TTF that are achieved by R-CVP appear comparable to the results obtained by CHOP alone. A substantially better outcome seems to be achieved by R-CHOP. Side effects and particularly severe granulocytopenia were less frequently encountered after CVP (14%) or R-CVP (24%) as compared to CHOP (53%) or R-CHOP (63%). However, clinically relevant infections were rare in both studies with 4% after CVP and R-CVP as compared to 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 the combination with Rituximab.

A third recently completed randomized study by the GLSG investigated the addition of Rituximab to a Fludarabine, Cyclophosphamide, Mitoxantrone (FCM) combination versus FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas.
Similar to the afore described results a significantly higher remission rate was observed after R-FCM as compared to FCM (79% versus 58%, p = 0.01). In addition, the duration of remission was significantly prolonged (16 months versus 10 months, p = 0.0381) and even more importantly a significantly longer overall survival was achieved (median not reached versus 24 months, p = 0.0030) (29).

These studies consistently show that the addition of Rituximab to chemotherapy is associated with an improved outcome of patients with advanced stage follicular lymphoma. However, the type of regimen to which Rituximab is added most probably has an important impact on patient outcome and needs to be further defined by subsequent prospective randomized studies.

Two findings of the current trial suggest that R-CHOP may have long lasting beneficial effects and may even lead to an improvement of overall survival. Hence, in spite of a relatively short observation time and a low overall mortality, a significant prolongation of survival was observed. After three years, only six patients on the R-CHOP arm have died as compared to 17 cases treated with CHOP alone.

This data is further supported by the aforementioned prolongation of survival after R-FCM therapy for relapsed follicular and mantle cell lymphomas (29). A high proportion of patients with long lasting disease free and overall survival has also been observed by Czuczman et al. after R-CHOP therapy in a non-randomized phase II study overlooking a nine year follow up period (28).

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 Interferon alpha maintenance was significantly longer after R-CHOP therapy as compared to CHOP alone. This data strongly suggests that the application of Rituximab together with chemotherapy during initial therapy has a substantial influence on subsequent therapy in remission.
A recently completed study by the Eastern Cooperative Oncology Group (ECOG) investigated Rituximab maintenance after conventional cytoreductive therapy with CVP and showed a 2.7 year longer PFS after two years of Rituximab maintenance (37).

In two other studies Rituximab was applied as initial single agent therapy and in this setting a prolonged application proved superior over the “standard” schedule of 4 x 375 mg/m² (38,39). The data from all of these studies consistently show that Rituximab has a significantly beneficial effect in patients with advanced stage follicular lymphoma either when given in addition to initial chemotherapy or as maintenance after cytoreductive therapy without Rituximab or by prolonged application as a single agent. It is therefore no longer the question whether Rituximab should be applied for first line therapy of advanced stage follicular lymphomas but rather how. 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 complementary and 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 biological risk factors. In this context R-CHOP may be the preferred treatment option in patients with advanced stage symptomatic disease in whom a high remission rate and a long lasting remission are the primary goals of therapy.
References


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 mantel cell Lymphomas – results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2004;104: 3064-71


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Front-line therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) significantly improves the outcome of patients with advanced stage follicular lymphomas as compared to CHOP alone - results of a prospective randomized study of the German Low Grade Lymphoma Study group (GLSG)

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