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)

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Short title: Immuno-Chemotherapy in relapsed FL and MCL
Category: Clinical observation, interventions, and therapeutic trials

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Acknowledgement:
This work was in part supported by a grant of the Deutsche Krebshilfe
ABSTRACT

In follicular lymphoma (FL) and mantle cell lymphoma (MCL) the monoclonal antibody Rituximab may improve the prognosis when combined with chemotherapy. This was investigated in a prospective randomized study in patients with relapsed disease. 147 patients were randomized to receive 4 courses of chemotherapy with fludarabine 25 mg/m² d 1-3, cyclophosphamide 200 mg/m² d 1-3 and mitoxantrone 8 mg/m² d1 (FCM) alone or combined with Rituximab (375 mg/m²) (R-FCM). Of 128 evaluable patients 62 were randomized for FCM and 66 for R-FCM. R-FCM revealed an overall response rate of 79% (33% CR, 45% PR) as compared to 58% for FCM alone (13% CR, 45% PR; p=0.01), with similar results in a subgroup analysis of FL (94% vs. 70%) and MCL (58% vs. 46%). In the total group, the R-FCM arm was significantly superior concerning progression-free (PFS) (p=0.0381) and overall survival (OS) (p=0.0030). In FL PFS was significantly longer in the R-FCM arm (p=0.0139) while in MCL a significantly longer OS was observed (p=0.0042). There were no differences in clinically relevant side effects in both study arms. Hence, the addition of Rituximab to FCM chemotherapy significantly improves the outcome of relapsed or refractory FL and MCL.

INTRODUCTION

Follicular lymphomas (FL) and mantle cell lymphomas (MCL) represent two challenging malignant diseases for clinicians, pathologists and basic researchers. Both cannot be cured by conventional therapeutic approaches and are characterized by a high initial response rate to chemotherapy which is followed by repeated recurrences. FL is frequent and accounts for approximately 20 – 25% of all lymphomas. It maintains a sensitivity to chemotherapy over a prolonged period of time before becoming ultimately resistant or transforming into a high grade lymphoma. The median survival is in the range of 8 – 10 years. MCL is relatively rare
comprising 5 – 11% of all lymphomas. In contrast to almost all other lymphomas it becomes rapidly resistant to chemotherapy and has the worst prognosis with a median survival of only 3 to 4 years and very few long term survivors. 2,3 In both lymphomas little therapeutic progress has been achieved within the last decades and the survival of patients has remained almost unchanged over the last 50 years. 1

New therapeutic perspectives have recently arisen which justify the hope for a substantial improvement of prognosis. They include myeloablative therapy followed by peripheral stem cell transplantation in younger patients as indicated by a series of phase II studies.6-8 Two recently completed prospective randomized phase III trials by the German Low Grade Lymphoma Study Group (GLSG) and the European MCL Intergroup showed a significant prolongation of the event free interval by myeloablative radiochemotherapy with subsequent stem cell transplantation as consolidation therapy in patients with FL and MCL achieving a complete or partial remission by initial cytoreductive chemotherapy.9,10 This approach is restricted, however, to younger patients and potentially hampered by the risk of secondary leukemias and myelodysplastic syndromes.11,12 More specific, less toxic and more broadly applicable treatment modalities are therefore warranted.

Monoclonal antibodies (mAB) offer such a new and more targeted approach. They may be applied as anti-idiotype AB,13 as carriers for toxins or radioisotopes14-17 or as direct cytotoxic agents with an inherent antilymphoma activity.

The latter approach has gained increasing clinical relevance through the development of the chimeric human-mouse anti-CD20 mAB Rituximab. This is a human IgG1κ antibody with variable regions isolated from a murine anti-CD20 monoclonal antibody. In vitro studies showed that Rituximab is able to lyse CD20+ cells by complement activation or antibody-dependent cell-mediated cytotoxicity.18 Other potential mechanisms of action include the induction of apoptosis, a block of the G1S-transition, an impairment of differentiation and an increased phosphorylation of cellular proteins.19
CD20 is expressed on normal B cells and most malignant B cell lymphomas and is essential for the regulation of cell cycle and differentiation.\textsuperscript{20} Several phase II trials have shown that Rituximab has a high to moderate single agent activity in pretreated patients with FL and MCL.\textsuperscript{21-26} These promising data prompted the application of Rituximab at earlier stages of therapy\textsuperscript{27,28} and several phase II studies revealed high remission rates of more than 90\%.\textsuperscript{29-31} The benefit of Rituximab could recently be further demonstrated by a prospective randomized trial of CHOP plus Rituximab versus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) alone in elderly patients with aggressive lymphomas.\textsuperscript{32} In FL and MCL results of prospective randomized trials have so far not been available and are warranted to better judge the clinical impact of this approach. Hence, the GLSG embarked on a prospective randomized trial of Rituximab in combination with chemotherapy versus chemotherapy alone in patients with relapsed or refractory FL and MCL. Since these patients had received standard CHOP therapy for first line treatment, the new combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) was chosen as therapeutic baseline. This protocol was introduced by Bosch et al. who reported a remission rate of 57\% and 61\% in heavily pretreated patients with relapsed or refractory FL or CLL, respectively.\textsuperscript{33}

**PATIENTS AND METHODS**

**Patients and Entry Criteria**

This study was performed as a prospective, randomized, open-label multicenter phase III trial. It was started in 1998 and included patients of ages 18 years and older with relapsed or refractory follicular, mantle cell or lymphoplasmocytoid lymphoma according to the WHO classification.\textsuperscript{34} Entry criteria comprised a non-response or relapse after at least one preceding
chemotherapy as well as recurrence after autologous stem cell transplantation. The histologic specimens underwent a central review at one of six designated pathology reference centers. Pregnant or lactating women and patients of childbearing potential not using a reliable contraceptive method were not allowed to enroll.

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**

Patients were enrolled in the study by the responsible physician after giving their written informed consent. All patients underwent a central randomization procedure at the studycenter by telephone. Randomization was done by a computer program stratified for histology, response to the preceding chemotherapy and the number of previous therapies using the method of random permutated blocks.

The FCM combination comprised fludarabine 25 mg/m²/d over 30 minutes i.v. on days 1-3, cyclophosphamide 200 mg/m²/d as a four hour infusion on days 1-3 and mitoxantrone 8 mg/m²/d over 30 minutes i.v. on day 1. Treatment cycles were repeated after every four weeks for a total of four cycles. In patients with peripheral lymphocyte counts > 20000/mm³ and /or a larger tumor mass, i.e. bulky disease > 10 cm, a cytoreductive pre-phase could be performed, comprising cyclophosphamide at a dose of 200 mg/m² as a one hour infusion over 3 to 5 days.

Patients who were randomized into the R-FCM arm received a dose of 375 mg/m²/d Rituximab on the day before the respective FCM course. Patients achieving a complete or partial remission after FCM or R-FCM, respectively, underwent a subsequent randomization for two courses of Rituximab to be given 3 and 6 months after completion of salvage therapy
versus observation only. Courses of Rituximab consisted of four doses of 375 mg/m²/d given at four consecutive weeks. This second randomization was stratified for the type of salvage therapy with FCM or R-FCM, the response to this treatment (CR or PR) and histology.

**Evaluation and Response Criteria**

Response to therapy was assessed after the first two cycles of FCM or R-FCM and 4 weeks after the completion of the fourth course. Subsequent follow-up was done in intervals of 3 months. Response evaluation comprised a physical examination, 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.

Response was defined according to the International Working Group criteria. 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. The appearance of new nodal or extranodal manifestations or the enlargement of preexisting lymphoma manifestations by more than 25% were considered as progression. Event free interval was defined from the end of successful therapy to documentation of progression or death, time to progression as the interval between the start of treatment and documentation of progressive disease and survival as the interval between enrolment into the study to death. The frequency and severity of side effects was recorded according to NCIC Common Toxicity Criteria (CTC).

**Statistics**

The comparison of FCM alone vs. FCM with Rituximab was designed to test whether the addition of Rituximab could increase the remission rate of 57% for FCM alone as reported by Bosch et al by 20%. On this basis a one-sided triangular sequential test with a working
significance level of 0.05 was applied. This procedure allowed to detect the assumed superiority of FCM and Rituximab over FCM alone with a probability of 95% and also allowed to stop the recruitment as soon as the level of significance was reached. The sequential procedure was designed to be equivalent in power and working significance level to a fixed sample test with 228 observations. A further explorative analysis was done on an intention to treat basis for histological subgroups, the progression free survival after start of therapy and the overall survival using the Fisher-Test for binary responses and the Logrank-test and univariate Cox-regression for time-censored observations.

A second question of the current trial addressed the impact of two additional cycles of Rituximab applied at 3 and 6 months in remission as compared to observation only on the progression free interval. At the time of this analysis enrollment into the second part of the study is ongoing. Hence, the current report concentrates on the comparison of FCM versus R-FCM only.

**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 committees of the participating institutions.

**RESULTS**

One hundred and forty-seven patients from 61 participating institutions of the GLSG were enrolled into the trial between November 1998 and June 2001. At this time the applied one sided sequential test showed a significant advantage for the R-FCM arm and further randomization was stopped (Fig. 1). In detail the following results were obtained:
Patients Characteristics

Of the 147 patients 93 (63%) cases were registered as FL, 40 (27%) patients were registered as MCL and 14 (10%) patients presented initial with a lymphoplasmocytic/cytoid lymphoma. After correction by reference histology 72 (49%) patients had a FL, 52 (35%) patients had a MCL and 16 (11%) patients were diagnosed as lymphoplasmocytic/cytoid lymphoma. There were also five patients diagnosed as diffuse large B-cell lymphoma and two patients were diagnosed as classical B-CLL by reference histology. 128 cases (62 randomized for FCM, 66 randomized for R-FCM) were documented and evaluable for response to therapy and toxicity at the time of this report. In 10 patients the documentation was incomplete and 9 patients (4 randomized for FCM and 5 for R-FCM) were withdrawn immediately after randomization without start of therapy.

The median age in this group was 62.5 years, with a range from 35 to 80 years. Sixty-three percent of cases were 60 years of age or older. All patients had advanced stage disease of stages III or IV before entering the study. All patients had received at least one previous chemotherapy. The median time from initial diagnosis to study entry was 2 years. Table 1 summarizes the main patient characteristics and indicates a balanced distribution between the two treatment arms.

Table 1 Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>all Patients</th>
<th>FL</th>
<th>MCL</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>FCM</td>
<td>R-FCM</td>
<td>FCM</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (years)/Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61.5</td>
<td>63.5</td>
<td>59.5</td>
</tr>
<tr>
<td></td>
<td>(35-77)</td>
<td>(42-80)</td>
<td>(35-77)</td>
</tr>
<tr>
<td><strong>Age&gt;60 years</strong></td>
<td>38 (61%)</td>
<td>42 (64%)</td>
<td>15 (50%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (58%)</td>
<td>39 (59%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (42%)</td>
<td>27 (41%)</td>
<td>17 (57%)</td>
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Table 1  Patients Characteristics (continued)

<table>
<thead>
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<th>FL</th>
<th>MCL</th>
</tr>
</thead>
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<tr>
<td></td>
<td>FCM</td>
<td>R-FCM</td>
<td>FCM</td>
</tr>
<tr>
<td>No. of previous therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56 %</td>
<td>59 %</td>
<td>53 %</td>
</tr>
<tr>
<td>2</td>
<td>27 %</td>
<td>27 %</td>
<td>30 %</td>
</tr>
<tr>
<td>&gt;2</td>
<td>16 %</td>
<td>14 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Previous PBCT</td>
<td>6 %</td>
<td>12 %</td>
<td>13 %</td>
</tr>
<tr>
<td>Remission to prior therapy</td>
<td>84 %</td>
<td>80 %</td>
<td>90 %</td>
</tr>
<tr>
<td>Extranodal involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>66 %</td>
<td>64 %</td>
<td>55 %</td>
</tr>
<tr>
<td>Liver</td>
<td>4 %</td>
<td>8 %</td>
<td>4 %</td>
</tr>
<tr>
<td>GI tract</td>
<td>12 %</td>
<td>14 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Spleen</td>
<td>30 %</td>
<td>29 %</td>
<td>23 %</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>24 %</td>
<td>32 %</td>
<td>30 %</td>
</tr>
<tr>
<td>LDH elevated</td>
<td>30 %</td>
<td>25 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FL</td>
<td>30 (48 %)</td>
<td>35 (53 %)</td>
<td>30</td>
</tr>
<tr>
<td>MCL</td>
<td>24 (39 %)</td>
<td>24 (36 %)</td>
<td>-</td>
</tr>
<tr>
<td>IC</td>
<td>8 (13 %)</td>
<td>6 (9 %)</td>
<td>-</td>
</tr>
<tr>
<td>B-CLL</td>
<td>0 (0 %)</td>
<td>1 (2 %)</td>
<td>-</td>
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</table>

Treatment Results

Fiftyseven patients in each arm of the 128 evaluable documented patients were treated according to protocol. In the R-FCM treated group there were 21 patients who finished therapy with a CR and 26 patients who finished with a PR (OR: 82%). In the group treated with FCM alone 8 patients finished with a CR and 27 patients achieved a PR (OR: 61%). According to the sequential nature of the monitoring test, this shows a significant improvement for the combination therapy (p=0.0064) in the per protocol analysis.
Five patients randomized for FCM did not complete the scheduled 4 treatment cycles without showing any progression of the lymphoma. Four patients stopped therapy after 3 cycles (one patient with PR, one with MR and two with stable disease.) One other patient stopped therapy with stable disease after 2 cycles. In the R-FCM group in one patient the diagnosis was changed to B-CLL after the first course and therapy was stopped with stable disease. One patient randomized for R-FCM died during the first cycle of therapy and no antibody was given because of an administrative error. Six other patients of the R-FCM group did also not complete the scheduled 4 treatment cycles. One patient stopped therapy after 2 cycles in CR, 4 patients after 3 cycles in PR and one patient revealed a stable disease after 2 cycles. In one patient with stable disease after 3 cycles no further staging was done. This patient was evaluated like having a stable disease after therapy. All of these patients were included in the following evaluation on an intention to treat basis using the last reported treatment result and the corrected histology for subgroup analysis.

An overall response rate (CR plus PR) of 69%, and a complete remission rate of 23% was achieved for the whole group. There was a significant advantage for the R-FCM treated patients with an overall response rate of 79% as compared to 58% in the FCM alone arm.
(p = 0.01). Similarly, a higher CR rate was observed in the R-FCM group (33% vs. 13%; p = 0.005) (Table 2).

**Table 2** Response rates for FCM and R-FCM (intention to treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>FCM</th>
<th>R-FCM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluable patients</strong></td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>CR</td>
<td>8 (13%)</td>
<td>22 (33%)</td>
</tr>
<tr>
<td>PR</td>
<td>28 (45%)</td>
<td>30 (45%)</td>
</tr>
<tr>
<td>MR</td>
<td>4 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>PD</td>
<td>16 (26%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>EX</td>
<td>3 (5%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>CR+PR</td>
<td>36 (58%)</td>
<td>52 (79%)</td>
</tr>
</tbody>
</table>

CR = complete remission;
PR = partial remission;
MR = minor response;
SD = stable disease;
PD = progressive disease;
EX = death

Separate analysis of FL and MCL revealed a substantial benefit for R-FCM in both lymphoma subtypes with overall response rates of 94% vs. 70% (p = 0.011) for FL and of 58% vs. 46% (p = 0.282) for MCL (Table 3). R-FCM was superior to FCM in all analyzed subgroups comprising patients having received less than 2 prior therapies (OR 82% vs 71%) or 2 and more prior therapies (OR 74% vs 41%) as well as in patients with refractoriness against the preceding therapy (OR 62% vs 20%).

After a median observation time of 18 months (range 1 – 43 months) the estimated overall survival (OS) of all patients is 63% at two years and the estimated median progression free
R-FCM was superior to FCM in both lymphoma subtypes. In FL the overall response rate (CR and PR) was 94% versus 70% (p=0.011), in MCL it was 58% versus 46% (p=0.282).

CR = complete remission; PR = partial remission; MR = minor response; SD = stable disease; PD = progressive disease; EX = death
53%) on the FCM arm. This result was not or only marginally influenced by the second randomization since the randomization for Rituximab versus observation was balanced for therapy with R-FCM or FCM. Still, it cannot be completely ignored that an improved initial therapy by R-FCM may have an impact on subsequent treatment and long term outcome. This question is addressed by the ongoing randomization for treatment in remission.

Figure 2: Progression free survival (Panel a) and overall survival (Panel b) after start of therapy for FCM or R-FCM

![Progression free survival (Panel a) and overall survival (Panel b) after start of therapy for FCM or R-FCM](image)

The estimated median PFS is 16 months for R-FCM as compared to 10 months for FCM (p=0.0381). The median OS is not reached for R-FCM as compared to 24 months (estimated) for FCM (p=0.0030).

Separate analysis of FL and MCL revealed a beneficial effect of R-FCM in both lymphoma subgroups. In FL the median PFS for R-FCM randomized patients was not reached at 3 years while the estimated median was 21 months for FCM treated cases (p=0.0139). In both groups the medians for OS were not reached yet. At two years 16 patients on the R-FCM arm (estimated OS 90%) were still alive as compared to 7 cases (estimated OS 70%) randomized for FCM alone (p=0.0943) (Fig. 3a). In MCL the respective medians for the PFS were 8
months for R-FCM versus 4 months for FCM (p=0.3887). For R-FCM the median OS was not reached while the estimated median OS for the FCM group was 11 months (p=0.0042) (Fig. 3b). At two years 8 patients on the R-FCM arm (estimated OS 65 %) were still alive as compared to 4 cases (estimated OS 35 %) after therapy with FCM.

**Figure 3:** Overall survival (OS) after start of therapy for patients with follicular lymphomas (FL) (Panel a) and mantle cell lymphomas (MCL) (Panel b) randomized for FCM or R-FCM

In FL the median OS is not reached in both groups. At two years the estimated OS is 90% in R-FCM as compared to 70% on the FCM arm (p=0.0943). In MCL patients randomized for R-FCM the median OS is not reached as compared to 11 months (estimated) on the FCM arm (p=0.0042).

The group of lymphoplasmocytic/cytoid lymphomas that was entered into the study was too small to draw any meaningful conclusions. Still, the respective results are given to complete the overall description of the study results. From 14 evaluable patients with lymphoplasmocytic/cytoid lymphoma 6 patients were randomized for R-FCM and 8 patients
were randomized for FCM alone. The respective response rates are 83% for the R-FCM arm and 50% for the FCM arm.

**Side effects**

Treatment associated side effects comprised predominantly myelosuppression and granulocytopenia in particular (Table 4). Granulocytopenia of grade 3 and 4 occurred after 40% of all cycles with a comparable frequency in both treatment groups. Lymphocytopenia was more frequent in the R-FCM arm with 51% of courses experiencing grade 3 and 4 toxicity in contrast to only 39% of courses for FCM alone (p=0.006). These differences were of no clinical relevance, however, since they were not associated with an increased risk of infectious complications. WHO grade 3 or 4 infections occurred in only 1.5% of all courses and were not different between the two treatment arms. Non-hematologic side-effects consisted mainly of 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 predominantly after the first infusion. In 4 cases Rituximab therapy had to be terminated early because of severe allergic reactions. These patients were evaluated on an intention to treat basis in the R-FCM arm.

**Table 4 Side effects after treatment with FCM and R-FCM**

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<thead>
<tr>
<th></th>
<th>FCM</th>
<th>R-FCM</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1+2</td>
<td>Grade 3+4</td>
</tr>
<tr>
<td>Allergy</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Chill</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Exantheme</td>
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</tr>
<tr>
<td>Headache</td>
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<td>0.0</td>
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</table>
### Table 4  Side effects after treatment with FCM and R-FCM (continued)

<table>
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<th></th>
<th>R-FCM</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1+2 %</td>
<td>Grade 3+4 %</td>
<td>Grade 1+2 %</td>
<td>Grade 3+4 %</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>14.3</td>
<td>40.6</td>
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<tr>
<td>Hemoglobin</td>
<td>44.4</td>
<td>5.3</td>
<td>44.7</td>
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<tr>
<td><strong>Lymphocytes</strong></td>
<td>3.9</td>
<td>39.4</td>
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<td>51.2</td>
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<tr>
<td>Thrombocytes</td>
<td>33.3</td>
<td>11.3</td>
<td>30.8</td>
<td>11.7</td>
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<tr>
<td>Leukocytes</td>
<td>16.9</td>
<td>55.6</td>
<td>23.5</td>
<td>53.6</td>
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<tr>
<td>Infection</td>
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<td>Fever</td>
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<td>0.5</td>
<td>1.1</td>
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<td>Nausea/vomiting</td>
<td>22.1</td>
<td>0.0</td>
<td>17.8</td>
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<td>Mucositis</td>
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<td>0.6</td>
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<td>Cardiac dysfunction</td>
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<td>0.3</td>
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</tr>
<tr>
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</tr>
<tr>
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</table>

Side effects were comparable between both treatment arms with the exception of a higher frequency of lymphocytopenia after treatment with R-FCM (p=0.006). This difference was clinically irrelevant, however, since no increase in infectious complications was observed.
DISCUSSION

The current study is the first completed prospective randomised trial in low grade lymphomas comparing the efficacy of Rituximab plus chemotherapy versus chemotherapy alone. It clearly demonstrates a significant improvement of remission rates and more importantly of overall survival through the addition of Rituximab to the FCM regimen (R-FCM) over FCM alone in relapsed or refractory follicular (FL) and mantle cell lymphomas (MCL). Based on preceding phase II studies applying Rituximab with other cytostatic regimens and the trial by Bosch et al. reporting a response rate of 57% for FCM salvage therapy, the assumption was made that Rituximab might increase the overall response rate by 20%. This assumption could be confirmed with a response rate of 58% and 13% complete remissions in the chemotherapy alone arm as compared to 79% and 33% complete remissions in patients receiving R-FCM ($p = 0.01$). R-FCM was superior to FCM alone in all subgroups of patients that were included into this trial. Hence, a higher remission rate was achieved in FL (OR 94% vs. 70%) as well as in MCL (OR 58% vs 46%). In particular, R-FCM was more efficacious in patients with refractoriness against the preceding chemotherapy (OR 62% vs. 20%).

While the improved response rate in FL was somewhat expected from preceding phase II studies, the substantially higher rate of overall responses and of complete remissions in particular that was observed in MCL appears remarkable. This lymphoma subtype has a comparatively low to moderate sensitivity to chemotherapy. Responses to Rituximab alone were in the range of 30 – 35% only when applied for salvage therapy as well as when given for first line treatment. Hence, it may be speculated that the addition of Rituximab may render MCL cells more susceptible to subsequent chemotherapy possibly by enhancing the ability to undergo apoptosis. This assumption is indirectly supported by the finding that the beneficial effect of Rituximab when added to chemotherapy in high grade lymphomas appears to be restricted to cases with an overexpression of bcl 2.
Besides increasing the response rate to salvage therapy, it is most remarkable that the addition of Rituximab to FCM therapy prolonged the overall survival. For the total group of patients the addition of Rituximab to FCM chemotherapy in an univariate Cox-regression reduced the relative risk of death to 41% (95-CI: 22%, 75%) as compared to the chemotherapy alone group. This beneficial effect was most pronounced in patients with MCL showing a risk reduction to 31% (95-CI: 14%, 72%) while in FL the respective risk was reduced to 37% (95-CI: 11%, 124%). Considering the fact that the majority of previous studies have failed to show a prolongation of survival, these data are very encouraging. Although they should be confirmed by further investigations on Rituximab in combination with chemotherapy in both lymphoma subtypes, these data provide for the first time a clear evidence for the beneficial effect of Rituximab added to chemotherapy for FL and MCL. Hence, they justify the so far uncontrolled use of Rituximab in the respective indications as already frequently given by many individual physicians around the world.

In spite of these promising results it must be emphasised that the current data are restricted to patients with relapsed disease and to the combination of Rituximab with FCM chemotherapy. This setting was chosen since the current strategy by GLSG comprises a first line therapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) followed by a randomised comparison of myeloablative radiochemotherapy with stem cell transplantation versus interferon alpha maintenance.\(^9\) In this situation a fludarabine containing combination appeared most promising for salvage therapy. This assumption is supported by several clinical studies including the aforementioned report by Bosch et al.\(^{33,45-49}\)

In the current trial 58% remissions were obtained by FCM alone which is almost identical to the 57% response rate that was previously reported by Bosch et al. for heavily pretreated patients with relapsed or refractory FL. Hence, FCM represents a highly active combination which appears most suitable for the treatment of low grade lymphomas relapsing after prior therapy with a CHOP like regimen.
Since fludarabine was shown to induce a profound depression of CD4 lymphocytes leading to a long-lasting immune deficiency,\textsuperscript{50} the maximal number of cycles was limited to 4 courses. Through the addition of Rituximab a decrease of B-cells was expected as well, potentially resulting in an increased risk for infectious complications. Accordingly, a higher incidence of grade 4 lymphocytopenia was observed in patients receiving the R-FCM regimen. However, infectious complications were rare and occurred at a similar frequency in both arms with 6\% of courses experiencing grade 1 and 2 and 1.5\% of cycles with grade 3 and 4 infections. These data are comparable to other studies as well.\textsuperscript{29,33}

These data clearly indicate that the combination of Rituximab to FCM comprises a highly effective salvage therapy for relapsed or refractory follicular and mantle cell lymphomas.

Based on these results it is tempting to speculate on the impact of Rituximab for first line treatment in FL and MCL. So far, only results of phase II studies are available. When applied as a single agent at earlier stages of disease or in lymphomas with low tumor burden Rituximab induced remission rates from 40\% to 73\%.\textsuperscript{27,37,51} Emmanouilides et al. combined Rituximab with mitoxantrone and cyclophosphamide. Of 27 patients 20 achieved a complete response and 5 patients a partial response, for an overall response rate of 92\%.\textsuperscript{52} Even, a 100\% overall response rate with 58\% complete remissions was reported by Czuczman et al. combining Rituximab with CHOP.\textsuperscript{53} Similar data also emerged from a study by Howard and Rambaldi.\textsuperscript{31,54} Maloney et al. applied Rituximab as maintenance therapy with similar results and a progression free survival of 76\% at 2 years.\textsuperscript{55} In addition, McLaughlin et al. recently reported about safety data, when combining fludarabine, mitoxantrone and dexamethasone with Rituximab. All patients received a prophylaxis for Pneumocystis carinii and no increase in the rate of infectious complications was observed.\textsuperscript{56}
In spite of these encouraging data, the results of currently ongoing prospective randomized trials must be awaited before a final conclusion about the addition of Rituximab to front line chemotherapy can be drawn.

Presently it can therefore be concluded that the addition of Rituximab to FCM chemotherapy comprises a highly effective salvage regimen for relapsed and refractory follicular and mantle cell lymphomas which is superior to FCM chemotherapy alone. This combination may thus comprise a new standard for second line treatment of these diseases.

Acknowledgement

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 respectivly: R. Forstpointner, M. Dreyling, W. Hiddemann, Department of Internal Medicine III, Klinikum Großhadern, University of Munich; F. Fiedler, A. Hähnel, Department of Internal Medicine III, Klinikum Chemnitz; M. Gramatzki, Departement of Internal Medicine III, University of Erlangen; W.-D. Ludwig, H. Harder, Department of Hematology, Oncology and Tumorimmunology, Robert-Rössle-Klinik, Berlin; H.-J. Illiger, B. Metzner, Department of Internal Medicine II, Oncology and Hematology, Klinikum Oldenburg; M. Kneba, Department of Internal Medicine II, University of Schleswig-Holstein, Campus Kiel; M. Pfreundschuh, Department of Internal Medicine I, University of Homburg/Saar; R. Pasold, F. Rothmann, A. Haas, Department of Hematology and Oncology, Klinikum „Ernst-von-Bergmann“, Potsdam; H.J. Hurtz, R. Rohrberg, R. Behrends, Hämatologisch/Onkologische Praxis, Halle (Saale); H.P. Böck, H.E. Ballo, Hämatologisch/Onkologische Praxis, Offenbach; W.E. Berdel, Department of Internal Medicine A, University of Münster; K. Wilms, H. Rückle-Lanz, M.W. Wilhelm, Department of Internal Medicine, University of Würzburg; M.R. Clemens, Department of Internal
Franziskus Hospital, Bielefeld; P. Ketterer, O. Anders, Department of Oncology, Klinikum Südstadt, Rostock; L. Heidenreich, K.A. Jost, Department of Internal Medicine, Hematology/Oncology, Dreifaltigkeitshospital, Lippstadt; A. Franke, Department of Hematology and Oncology, Universitity of Magdeburg; H. Dürk, B. Schmid, S. Weibrecht, Department of Hematology/Oncology/Immunology, St.-Marien.Hospital, Hamm; R. Hehlmann, E. Lengfelder, I. Kottke, Department of Internal Medicine III, Klinik Mannheim, University of Heidelberg; G. Unverferth, W. Langer, F. Püschel, Department of Radiotherapy/Hematology, Kreiskrankenhaus, Aurich; M. Lößner, Department of Internal Medicine II, Carl-Thiem-Klinikum, Cottbus; J. Schimke, G. Jacobs, Hämatologisch/Onkologische Praxis, Saarbrücken; S. Vedder, J. Rövekamp, Department of Internal Medicine, St.-Christophorus-Krankenhaus, Werne; H.F. Hinrichs, B. Otremba, I. Zirpel, Hämatologisch/Onkologische Praxis, Oldenburg; G. Schliesser, Hämatologisch/Onkologische Praxis, Giessen; E. Höring, M. v. Ehr, M. Respondek, Hämatologisch/Onkologische Praxis, Stuttgart; M. Hahn, S. Müller, Hämatologisch/Onkologische Praxis, Ansbach; F. Busch, C. Lohse, Department of Internal Medicine, Klinikum Hof; J. Hotz, F. Marquard, Department of Gastroenterology, allgemeines Krankenhaus, Celle; T. Eisenhauer, H. Nolte, Department of Internal Medicine II, Städtisches Klinikum Kemperhofen, Koblenz; U. Karbach, M. Schröder, Department of Internal Medicine, Hematology/Oncology, Vinzentinus-Krankenhaus, Landau; W. Brugger, I. Funke, Department of Internal Medicine, Klinik Villingen; P. Hesse, Department of Internal Medicine, Asklepios Klinik, Parchim; M.J. Eckart, Hämatologisch/Onkologische Praxis, Erlangen; D. Guggenberger, D. Tummes, R. Weinberg, Hämatologisch/Onkologische Praxis, Aachen; M. Pauw, Department of Internal Medicine, Städt. Krankenhaus, Nettetal; C. Underhill, Medical Oncology, Murray Valley Private Hospital, Wogonda, Australia.
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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)

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