The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with 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

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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. A total of 147 patients were randomized to receive 4 courses of chemotherapy with 25 mg/m^2 fludarabine on days 1 to 3, 200 mg/m^2 cyclophosphamide on days 1 to 3, and 8 mg/m^2 mitoxantrone on day 1 (FCM), alone or combined with rituximab (375 mg/m^2; 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% complete remission [CR], 45% partial remission [PR]) as compared with 58% for FCM alone (13% CR, 45% PR; $P = .01$), 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 survival (PFS; $P = .0381$) and overall survival (OS; $P = .0030$). In FL PFS was significantly longer in the R-FCM arm ($P = .0139$) whereas in MCL a significantly longer OS was observed ($P = .0042$). 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. (Blood. 2004;104:3064-3071)

Introduction

Follicular lymphomas (FLs) and mantle cell lymphomas (MCLs) represent 2 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.[1-3] FL is frequent and accounts for approximately 20% to 25% of all lymphomas.[4] 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 to 10 years.[1,5] MCL is relatively rare, comprising 5% to 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 3 decades and the survival of patients has remained almost unchanged over the last 50 years.[1]

New therapeutic perspectives have recently arisen that 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 2 studies.[6-8] The German Low-Grade Lymphoma Study Group (GLSG) and the European MCL Intergroup recently completed 2 prospective randomized phase 3 trials that 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 is 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 (mABs) offer such a new and more targeted approach. They may be applied as anti-idiotype ABs,[13] as carriers for toxins or radioisotopes,[14-17] 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

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mAB rituximab. This is a human immunoglobulin G1 (IgG1) antibody with variable regions isolated from a murine anti-CD20 mAB. 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 G_1/S-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.[20]

Several phase 2 trials have shown that rituximab has a high-to-moderate single agent activity in pretreated patients with FL and MCL.[21-26] These promising data prompted the application of rituximab at earlier stages of therapy,[27,28] and several phase 2 studies revealed high remission rates of more than 90%.[29-31] The benefit of rituximab could recently be further demonstrated by a prospective randomized trial of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) plus rituximab versus CHOP alone in elderly patients with aggressive lymphomas.[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. Because these patients had received standard CHOP therapy for first-line treatment, the new combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) was chosen as a therapeutic baseline. This protocol was introduced by Bosch et al[33] who reported a remission rate of 57% and 61% in heavily pretreated patients with relapsed or refractory FL or CLL, respectively.

Patients and methods

Patients and entry criteria

This study was performed as a prospective, randomized, open-label, multicenter phase 3 trial. It was started in 1998 and included patients age 18 years and older with relapsed or refractory follicular, mantle cell, or lymphoplasmocytoid lymphoma according to the World Health Organization (WHO) classification.[34] Entry criteria comprised a nonresponse or relapse after at least 1 preceding chemotherapy as well as recurrence after autologous stem cell transplantation. The histologic specimens underwent a central review at 1 of 6 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 computed tomographic (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 physician responsible for their care after giving their written informed consent. All patients underwent a central randomization procedure at the study center 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 25 mg/m^2 fludarabine per day given intravenously over 30 minutes on days 1 to 3, 200 mg/m^2 cyclophosphamide per day as a 4-hour infusion on days 1 to 3, and 8 mg/m^2 mitoxantrone per day given intravenously over 30 minutes on day 1. Treatment cycles were repeated after every 4 weeks for a total of 4 cycles. In patients with peripheral lymphocyte counts more than 20 000/mm^3 and/or a larger tumor mass (ie, bulky disease more than 10 cm) a cytoreductive pre-phase could be performed, comprising cyclophosphamide at a dose of 200 mg/m^2 as a 1-hour infusion over 3 to 5 days.

Patients who were randomized into the R-FCM arm received a dose of 375 mg/m^2 per day 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 2 courses of rituximab to be given 3 and 6 months after completion of salvage therapy versus observation only. Courses of rituximab consisted of 4 doses of 375 mg/m^2 per day given at 4 consecutive weeks. This second randomization was stratified for the type of salvage therapy with FCM or R-FCM, the response to this treatment (complete remission [CR] or partial remission [PR]), and histology.

Evaluation and response criteria

Response to therapy was assessed after the first 2 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.[35] Hence, CR comprised the elimination of all lymphoma manifestations for at least 4 weeks including the bone marrow, while 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 enrollment in the study to death. The frequency and severity of side effects were recorded according to the National Cancer Institute of Canada (NCIC) Common Toxicity Criteria (CTC).

Statistics

The comparison of FCM alone versus 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,[33] by 20%. On this basis, a 1-sided triangular sequential test with a working significance level of .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 histologic subgroups, the progression-free survival after start of therapy, and the overall survival using the Fisher test for binary responses and the log-rank test and univariate Cox regression for time-censored observations.

A second question of the current trial addressed the impact of 2 additional cycles of rituximab applied at 3 and 6 months in remission as compared with 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.

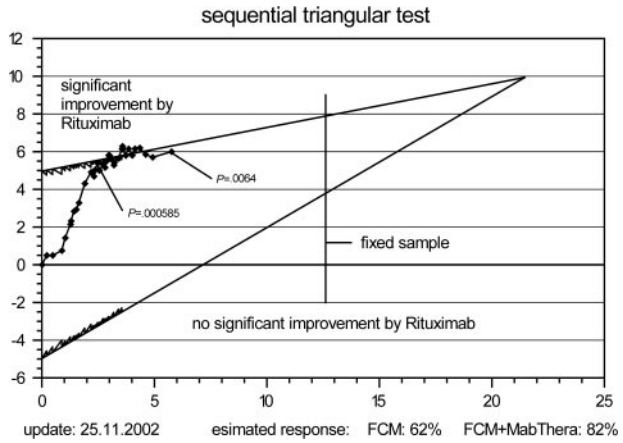

Figure 1. Development of the one-sided sequential test of FCM versus R-FCM over study time in patients treated according to protocol.

Results

Between November 1998 and June 2001, 147 patients from 61 participating institutions of the GLSG were enrolled into the trial. At this time, the applied one-sided sequential test showed a significant advantage for the R-FCM arm and further randomization was stopped (Figure 1).

Patient characteristics

Of the 147 patients, 93 (63%) were registered as having FL, 40 (27%) were registered as having MCL, and 14 (10%) initially presented with a lymphoplasmocytic/lymphoplasmacytoid lymphoma. After correction by reference histology, 72 (49%) patients had a FL, 52 (35%) patients had an MCL, and 16 (11%) patients were diagnosed as lymphoplasmocytic/cytoid lymphoma. There were also 5 patients diagnosed as diffuse large B-cell lymphoma and 2 patients were diagnosed as classical B-cell chronic lymphocytic leukemia (B-CLL) by reference histology. There were 128 patients (62 randomized for FCM, 66 randomized for R-FCM) who 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. In 63% of cases, patients 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 1 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 2 treatment arms.

Treatment results

Of the 128 evaluable documented patients, 57 patients in each arm 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 (overall response rate [OR]: 82%). In the group treated with FCM alone 8 patients finished with a CR and 27 patients archieved a PR (OR: 61%). According to the sequential nature of the monitoring test, this shows a significant improvement for the combination therapy ($P = .0064$) in the per-protocol analysis.

There were 5 patients randomized for FCM who did not complete the scheduled 4 treatment cycles without showing any progression of the lymphoma. There were 4 patients who stopped therapy after 3 cycles (1 patient with PR, 1 with minor response

Table 1. Patient characteristics

	All patients		FL		MCL	
	FCM	R-FCM	FCM	R-FCM	FCM	R-FCM
Age						
Median, y (range)	61.5 (35-77)	63.5 (42-80)	59.5 (35-77)	60 (42-80)	63 (42-77)	65 (49-75)
At least 60 y old, no. (%)	38 (61)	42 (64)	15 (50)	18 (51)	18 (75)	21 (88)
Sex, no. (%)						
Male	36 (58)	39 (59)	13 (43)	16 (46)	18 (75)	19 (79)
Female	26 (42)	27 (41)	17 (57)	19 (54)	6 (25)	5 (21)
No. of previous therapies, %						
1	56	59	53	66	63	50
2	27	27	30	23	21	33
More than 2	16	14	17	11	17	17
Previous PBCT, %	6	12	13	9	0	13
Remission to prior therapy, %	84	80	90	86	75	79
Extranodal involvement, %						
Bone marrow	66	64	55	49	70	77
Liver	4	8	4	9	5	10
GI tract	12	14	0	9	30	26
Spleen	30	29	23	20	47	39
B-symptoms, %	24	32	30	29	21	38
LDH elevated, %	30	25	17	23	43	26
Histologic subtype, no. (%)						
FL	30 (48)	35 (53)	30	35	NA	NA
MCL	24 (39)	24 (36)	NA	NA	24	24
IC	8 (13)	6 (9)	NA	NA	NA	NA
B-CLL	0 (0)	1 (2)	NA	NA	NA	NA

IC indicates lymphoplasmocytic/lymphoplasmacytoid lymphoma; NA, not applicable.

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

	FCM	R-FCM
No. of evaluable patients	62	66
CR, no. (%)	8 (13)	22 (33)
PR, no. (%)	28 (45)	30 (45)
MR, no. (%)	4 (6)	1 (2)
SD, no. (%)	3 (5)	3 (5)
PD, no. (%)	16 (26)	8 (12)
EX, no. (%)	3 (5)	2 (3)
CR+PR, no. (%)	36 (58)	52 (79)

R-FCM revealed a significantly higher overall response (CR and PR) of 79% versus 58% for FCM ($P = .01$) and a significantly higher CR rate of 33% versus 13% ($P = .005$).

CR indicates complete remission; PR, partial remission; MR, minor response; SD, stable disease; PD, progressive disease; and EX, death.

(MR), and 2 with stable disease). One other patient stopped therapy with stable disease after 2 cycles. In the R-FCM group, 1 patient's 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. There were 6 other patients in the R-FCM group who also did not complete the scheduled 4 treatment cycles. One patient stopped therapy after 2 cycles in CR, 4 patients stopped after 3 cycles in PR, and 1 patient revealed a stable disease after 2 cycles. In 1 patient with stable disease after 3 cycles no further staging was done. This patient was evaluated as 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% were 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 with 58% in the FCM alone arm ($P = .01$). Similarly, a higher CR rate was observed in the R-FCM group (33% vs 13%; $P = .005$; Table 2).

Separate analysis of FL and MCL revealed a substantial benefit for R-FCM in both lymphoma subtypes with overall response rates of 94% versus 70% ($P = .011$) for FL and of 58% versus 46% ($P = .282$) 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 2 years and the estimated median progression free survival is 13 months. As depicted by Figure 2A, a significant advantage for R-FCM was found for the progression-free survival (PFS) with an estimated median of 16 months as compared with 10 months for FCM ($P = .0381$). More important, the higher activity of R-FCM translated into a significant improvement of OS with the median not being reached at 3 years for patients randomized for R-FCM as compared with an estimated median survival of 24 months for patients randomized for FCM alone ($P = .0030$; Figure 2B). At 2 years, 26 patients (estimated OS: 73%) randomized for R-FCM were still alive as compared with 15 cases (estimated OS: 53%) on the FCM arm. This result was not or was 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 adressed by the ongoing randomization for treatment in remission.

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 whereas the estimated median was 21 months for FCM-treated cases ($P = .0139$). In both groups the medians for OS were not reached yet. At 2 years, 16 patients on the R-FCM arm (estimated OS: 90%) were still alive as compared with 7 cases (estimated OS: 70%) randomized for FCM alone ($P = .0943$; Figure 3A). In MCL, the respective medians for the PFS were 8 months for R-FCM versus 4 months for FCM ($P = .3887$). For R-FCM, the median OS was not reached, whereas the estimated median OS for the FCM group was 11 months ($P = .0042$; Figure 3B). At 2 years, 8 patients on the R-FCM arm (estimated OS: 65%) were still alive as compared with 4 cases (estimated OS: 35%) after therapy with FCM.

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 grades 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 grades 3 and 4 toxicity in contrast to only 39% of courses for FCM alone ($P = .006$). 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 2 treatment arms. Nonhematologic 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 3. Response rates for FCM and R-FCM for patients with follicular lymphomas and mantle cell lymphomas

	Follicular lymphoma (FL)		Mantle cell lymphoma (MCL)	
	FCM	R-FCM	FCM	R-FCM
No. of evaluable patients	30	35	24	24
CR, %	23	40	0	29
PR, %	47	54	46	29
MR, %	7	0	0	4
SD, %	7	0	0	8
PD, %	17	3	42	29
EX, %	0	3	13	0
PR + CR, %	70	94	46	58

R-FCM was superior to FCM in both lymphoma subtypes. In FL the overall response rate (CR and PR) was 94% versus 70% ($P = .011$); in MCL it was 58% versus 46% ($P = .282$).

CR indicates complete remission; PR, partial remission; MR, minor response; SD, stable disease; PD, progressive disease; and EX, death.

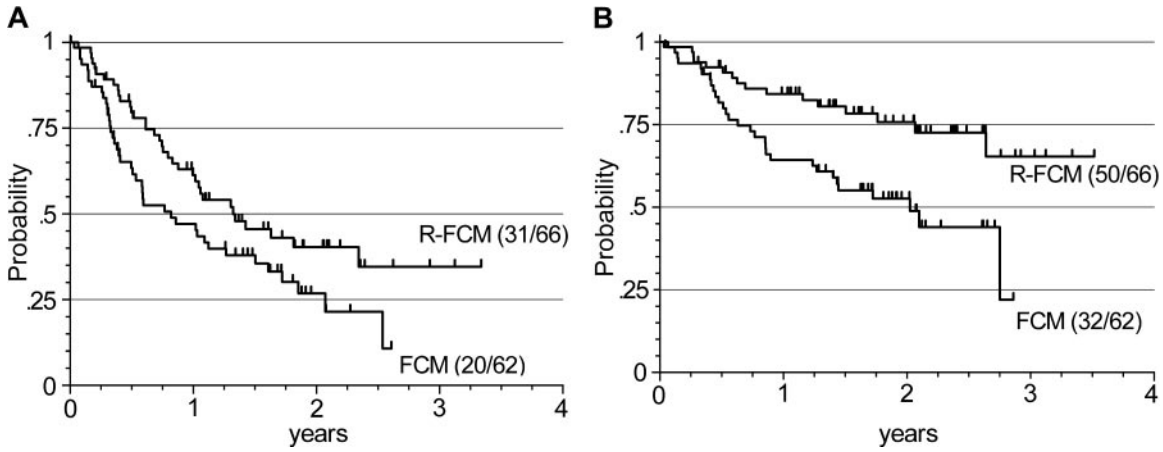

Figure 2. Progression-free survival and overall survival after start of therapy for FCM or R-FCM. (A) Progression-free survival; (B) overall survival. The estimated median PFS is 16 months for R-FCM as compared with 10 months for FCM ($P = .0381$). The median OS is not reached for R-FCM as compared with 24 months (estimated) for FCM ($P = .0030$).

Discussion

The current study is the first completed prospective randomized 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 important, of overall survival through the addition of rituximab to the FCM regimen (R-FCM) over FCM alone in relapsed or refractory FL and MCL. Based on preceding phase 2 studies applying rituximab with other cytostatic regimens,[36] and the trial by Bosch et al[33] 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 with 79% and 33% complete remissions in patients receiving R-FCM ($P = .01$). R-FCM was superior to FCM alone in all subgroups of patients that were included in 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 2 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% to 35% only when applied for salvage therapy as well as when given for first-line treatment.[26,37-39] 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.[40-44] 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 bcl2.

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 a univariate Cox regression analysis reduced the relative risk of death to 41% (95% confidence interval [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%) whereas in FL the respective risk was reduced to 37%

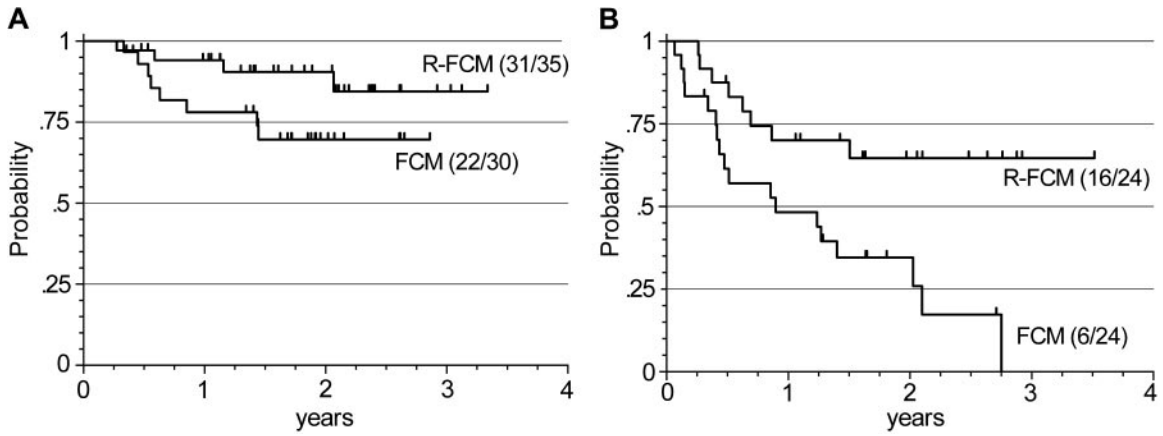

Figure 3. Overall survival after start of therapy for patients with follicular lymphomas and mantle cell lymphomas randomized for FCM or R-FCM. (A) Follicular lymphoma (FL); (B) mantle cell lymphoma (MCL). In FL the median overall survival (OS) is not reached in both groups. At 2 years the estimated OS is 90% in R-FCM as compared with 70% on the FCM arm ($P = .0943$). In patients with MCL randomized for R-FCM the median OS is not reached as compared with 11 months (estimated) on the FCM arm ($P = .0042$).

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

Side effect	FCM		R-FCM	
	Grades 1 + 2, %	Grades 3 + 4, %	Grades 1 + 2, %	Grades 3 + 4, %
Allergy	0.8	0.0	3.5	0.3
Chill	0.5	0.0	5.7	0.0
Exantheme	3.5	0.0	2.8	0.0
Headache	2.2	0.0	5.3	0.3
Granulocytes	14.3	40.6	18.7	39.6
Hemoglobin	44.4	5.3	44.7	5.9
Lymphocytes	3.9	39.4	10.3	51.2
Thrombocytes	33.3	11.3	30.8	11.7
Leukocytes	16.9	55.6	23.5	53.6
Infection	6.6	1.8	6.3	1.4
Fever	2.3	0.5	1.1	1.1
Nausea/vomiting	22.1	0.0	17.8	1.1
Mucositis	3.4	0.0	4.5	0.3
Diarrhea	0.5	0.5	3.9	0.6
Cardiac dysfunction	0.0	0.9	0.3	0.0
Neurotoxicity	1.1	0.1	0.8	0.2
Liver	3.1	0.0	5.2	0.0
Lactate dehydrogenase	6.2	0.0	6.3	0.3
Alopecia	10.7	7.1	10.5	3.7

Side effects were comparable between both treatment arms with the exception of a higher frequency of lymphocytopenia after treatment with R-FCM ($P = .006$). The difference was clinically irrelevant, however, because no increase in infectious complications was observed.

(95% CI: 11%-124%). Considering the fact that most 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 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 emphasized 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 randomized 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 a 58% remission rate was obtained by FCM alone, which is almost identical to the 57% response rate that was previously reported by Bosch et al[33] 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.

Because fludarabine was shown to induce a profound depression of CD4 lymphocytes, leading to a long-lasting immune deficiency,[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 lymphocytotopenia 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 grades 1 and 2 infections and 1.5% of cycles experiencing grades 3 and 4 infections. These data are comparable to other studies as well.[29,33]

These data clearly indicate that the combination of rituximab and 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 2 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%.[27,37,51] Emmanouilides et al[52] combined rituximab with mitoxantrone and cyclophosphamide. Of 27 patients, 20 achieved a complete response and 5 achieved a partial response, for an overall response rate of 92%.[52] A 100% overall response rate with a 58% complete remission rate was reported by Czuczman et al[53] combining rituximab with CHOP. Similar data also emerged from studies by Howard et al[31] and Rambaldi et al.[54] Maloney et al[55] applied rituximab as maintenance therapy with similar results and a PFS of 76% at 2 years. In addition, McLaughlin et al[56] 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.[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 that is superior to FCM chemotherapy alone. This combination may thus comprise a new standard for second-line treatment of these diseases.

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; F. Fiedler, A. Hähnel, Department of Internal Medicine III, Klinikum Chemnitz; M. Gramatzki, Department 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 Medicine, Mutterhaus der Borromäerinnen, Trier; H.W. Wandt, S. Fries, Department of Internal Medicine V, Klinikum Nord, Nürnberg; M. Planker, M. Busch, M. Hipp, Department of Internal Medicine II, städt. Krankenanstalten, Krefeld; D. Hennesser, Department of Internal Medicine, Vinzenz-Pallotti Hospital, Bergisch

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