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ORIGINAL REPORT

Rituximab Added to First-Line Mitoxantrone, Chlorambucil, and Prednisolone Chemotherapy Followed by Interferon Maintenance Prolongs Survival in Patients With Advanced Follicular Lymphoma: An East German Study Group Hematology and Oncology Study

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ABSTRACT

Purpose
Rituximab has been shown to be active in follicular lymphoma (FL), both as monotherapy and in combination with chemotherapy. We conducted a randomized trial comparing mitoxantrone, chlorambucil, and prednisolone (MCP) chemotherapy plus rituximab with MCP alone.

Patients and Methods
Previously untreated patients with stage III or IV CD20$^+$ indolent or mantle cell lymphoma were randomly assigned to either eight 28-day cycles of MCP plus rituximab (R-MCP; n = 181) or eight cycles of MCP alone (n = 177). All patients who achieved a complete or partial remission were treated with interferon maintenance until relapse. Herein, we report the results from the primary analysis population of patients with FL, who constituted the majority of patients (56%) recruited to the trial (n = 201; R-MCP, n = 105; MCP, n = 96).

Results
Rates of overall and complete response were significantly higher in the R-MCP arm than the MCP arm (overall response, 92% *v* 75%, respectively; $P = .0009$; complete response, 50% *v* 25%, respectively; $P = .004$). With a median follow-up time of 47 months, median event-free survival (EFS) and progression-free survival (PFS) times were significantly prolonged with R-MCP compared with MCP (EFS, not reached *v* 26 months, respectively; $P < .0001$; PFS, not reached *v* 28.8 months, respectively; $P < .0001$), and overall survival (OS) was significantly improved with R-MCP compared with MCP (4-year OS rate, 87% *v* 74%, respectively; $P = .0096$).

Conclusion
The R-MCP regimen significantly improves complete and overall response rates, EFS, PFS, and OS in patients with previously untreated advanced FL, without a clinically significant increase in toxicity.

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INTRODUCTION

Patients with follicular lymphoma (FL), the most common form of indolent non-Hodgkin's lymphoma (NHL),[1] have a median survival time of 6 to 10 years and a pattern of repeated relapses, generally with progressively shorter periods of remission between each relapse.[2,3] For patients with advanced FL requiring treatment, the use of combination chemotherapy and prolonged therapy has been shown to improve response rates and extend first remission compared with short-term alkylating agents alone but with no improvement in overall survival (OS).[4] Intensive nonmyeloablative chemotherapy can achieve clinical and molecular remission but with no evidence of cure.[5]

Although the use of myeloablative chemotherapy with autologous stem-cell support has been shown to confer a disease-free and OS advantage compared with conventional chemotherapy in patients with relapsing FL,[6] the value of this approach in the first-line setting remains less clear. In a recent study comparing high-dose therapy followed by purged autologous stem-cell transplantation with

cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy followed by interferon in patients with newly diagnosed advanced FL, the high-dose therapy group achieved higher response rates and longer median event-free survival (EFS). However, this did not translate into a better survival rate because of an excess of secondary malignancies.[7]

The chimeric monoclonal antibody rituximab binds avidly to the CD20 antigen, which is expressed on almost all malignant B cells.[8] Patients with heavily pretreated indolent NHL receiving rituximab monotherapy achieved an overall response rate (ORR) of 48% with low levels of toxicity.[9] Rituximab can sensitize NHL cells to a range of chemotherapeutic agents.[10,11] For instance, in the first ever study combining rituximab with CHOP, the ORR in patients with indolent NHL was 100%, and this translated into excellent long-term outcomes, with a median time to progression of 82.3 months.[12,13] In a recently published phase III study of rituximab plus CHOP versus CHOP alone in FL patients, the addition of rituximab to CHOP significantly improved ORR compared with CHOP alone (96% *v* 90%, respectively; $P = .011$), and after a median follow-up time of 18 months, the risk of treatment failure was significantly reduced ($P < .0001$). Estimated 2-year survival rates were 95% for rituximab plus CHOP and 90% for CHOP alone ($P = .016$).[14]

The combination of mitoxantrone, chlorambucil, and prednisolone (MCP) has been shown to be effective and well tolerated in patients with indolent NHL.[15,16] Because rituximab can enhance the cytotoxicity of both mitoxantrone and glucocorticosteroids in vitro[17,18] and has no overlapping toxicities, the addition of rituximab to MCP chemotherapy might be expected to enhance the efficacy of this regimen without significantly increasing toxicity. For these reasons, we initiated a multicenter, randomized phase III trial comparing the efficacy and toxicity of the standard MCP chemotherapeutic regimen with the combination of rituximab and MCP (R-MCP) in patients with previously untreated indolent NHL and mantle cell lymphoma (MCL).

PATIENTS AND METHODS

Patients

Patients were eligible for inclusion onto the study if they were aged between 18 and 75 years and had untreated, histologically confirmed, $CD20^+$ indolent NHL (FL, grade 1 and 2 only; lymphoplasmacytic lymphoma) and MCL. All patients were required to have stage III or IV disease according to the Ann Arbor classification and a general performance status of ≤ 2 according to the Eastern Cooperative Oncology Group scale.

Patients were required to be in need of therapy defined by the presence of at least one of the following criteria: "B" symptoms or extranodal manifestation; hematopoietic insufficiency (hemoglobin < 10 g/dL and/or platelets $< 100{,}000/\mu$L); rapid tumor growth (doubling of the product of the end-to-end diameters of the measurable lymphoma manifestation within 6 months); bulky disease (lymphoma > 7.5 cm in diameter; mediastinal tumor $>$ one third of thorax diameter at thoracic vertebra 5/6); or immunohematologic phenomena (eg, hemolytic anemia or immune thrombocytopenia). Patients with concomitant diseases and/or restricted organ function not caused by lymphoma or patients with HIV infection were excluded from the study. The histologic diagnosis had to be centrally confirmed by a designated reference pathologist.

The study complied with all of the requirements of the Declaration of Helsinki and its current amendments and was conducted in accordance with good clinical practice guidelines. All patients gave written informed consent. The protocol and accompanying materials were approved by an independent ethics committee and the local ethics committees at each participating center. The study has been registered as East German Study Group Hematology and Oncology Trial 39 and at ClinicalTrials.gov (http://www.clinicaltrials.gov/) under ID 00269113.

Random Assignment

Eligible patients were assigned at trial entry to treatment with either MCP or R-MCP. Random assignment was performed centrally using a randomization list, with patients stratified according to histologic status.

Treatment

Patients randomly assigned to treatment with MCP received a combination of mitoxantrone 8 mg/m^2 intravenously (IV) on days 1 and 2; chlorambucil 3×3 mg/m^2 orally (PO) on days 1 to 5; and prednisolone 25 mg/m^2 PO on days 1 to 5. Patients treated with R-MCP received rituximab 375 mg/m^2 IV on day 1 of each therapy cycle, followed by mitoxantrone (8 mg/m^2 IV) on days 3 and 4, chlorambucil (3×3 mg/m^2 PO) on days 3 to 7, and prednisolone (25 mg/m^2 PO) on days 3 to 7.

If a grade 3 or 4 rituximab-induced infusion reaction occurred, therapy was interrupted. All symptoms had to resolve or decrease in severity to grade 1 before rituximab was continued or MCP was started.

Patients were treated every 28 days for a maximum of eight cycles. MCP dosages were reduced by 25% for mitoxantrone and chlorambucil if severe myelosuppression occurred (leukocyte and/or platelet levels reduced to $< 1.0 \times 10^9$/L and $< 75 \times 10^9$/L, respectively).

Maintenance therapy with interferon alfa-2a (4.5 MU three times per week until relapse) was planned in all study patients with FL who had achieved partial remission (PR) or complete remission (CR) and was initiated within 4 to 8 weeks after treatment completion. After completion of induction treatment, patients were observed every 8 weeks during the first year, at 3-month intervals during the second year, and then every 6 months from the third year onward.

Response to Treatment and Adverse Events

The primary end point was remission rate, which was defined as the rate of CR and PR after induction therapy. CR required complete resolution of all disease symptoms, including lymph node swellings, hepatomegaly, and splenomegaly recorded at study entry and normalization of blood counts for a minimum of 4 weeks. In patients with initial lymphoma infiltration of the bone marrow, CR had to be confirmed by bone marrow biopsy. Any unconfirmed CRs were classified as PRs. PR was defined as $\geq 50\%$ decrease of all measurable/assessable lymphoma manifestations and normalization of blood counts for a minimum of 4 weeks, without occurrence of new lymphoma manifestations. Progressive disease (PD) was defined as an increase in tumor burden or splenomegaly by 25% or more or the appearance of new tumor lesions. Patients were classified as having no change if they did not have CR, PR, or PD.

Secondary efficacy parameters included progression-free survival (PFS; interval from random assignment date to progression of disease or death from NHL), OS (interval from random assignment date to death from any cause), and toxicity (graded in accordance with the National Cancer Institute of Canada Common Toxicity Criteria grading system).[19] Other efficacy parameters assessed included EFS (interval from random assignment date to treatment failure, which was defined as PD after two cycles and failure to achieve at least PR at cycle 6, disease progression, relapse, or death from any cause), duration of response (interval from first assessment of CR or PR to disease progression), and time to next antilymphoma treatment (interval from random assignment date to the time when new treatment was initiated).

Tumor responses were assessed after two treatment cycles, after six treatment cycles, and 4 weeks after completion of study treatment. Response assessment included all diagnostic measures used in the pretherapeutic staging (including computed tomography scans of neck, chest, abdomen, and pelvis and bone marrow biopsy). Patients with disease progression after two cycles of therapy were prematurely withdrawn from study treatment and were considered as having treatment failure in the analysis of EFS. Patients who had not reached a PR or CR after six cycles of therapy were also classified as experiencing treatment failure in the EFS analysis. Patients with a CR or a PR after six cycles of chemotherapy or immunochemotherapy, respectively, received a

further two consolidation cycles of MCP or R-MCP for a total of eight treatment cycles.

Statistical Analysis

The primary end point of the trial according to the protocol was ORR (CR + PR). Although the protocol allowed the inclusion of patients with FL, lymphoplasmacytic lymphoma, and MCL, the primary analysis population was defined as the population of FL patients. Efficacy analyses for patients with MCL and lymphoplasmacytic lymphoma were preplanned as exploratory analyses. Although the primary end point was response rate, the study sample size was calculated using the end point of PFS after 4 years. In patients with FL, a 4-year PFS rate of 45% was assumed for patients after treatment with MCP. It was calculated that 216 patients with FL, randomly assigned in a ratio of 1:1 between the study arms, would provide 80% power at a two-tailed significance level of 5% to detect an anticipated increase in the 4-year PFS rate by 20% to 65% after treatment with R-MCP. Two preplanned interim analyses were conducted; the first analysis was conducted after 50 patients were randomly assigned, and the second analysis was conducted after 124 patients were randomly assigned; a predefined P value of .0001 was used for each interim analysis. The main efficacy analysis of the primary end point of remission rate was planned after all randomly assigned patients completed induction therapy. Because the primary end point of the study was reached in the main analysis, one updated analysis with longer follow-up (47 months) on time-dependent parameters (PFS, EFS, OS, and others) was conducted. A final analysis is planned after all patients have completed a follow-up period of 4 years.

Statistical analysis of the difference in remission rates between treatment groups was undertaken using a two-sided Fisher test with $\alpha = .05$ (null hypothesis: remission rate for R-MCP was equal to that for MCP alone; alternative hypothesis: there was a statistically significant difference in remission rates between the two treatment arms). PFS and OS after 4 years of follow-up were to be analyzed by the log-rank test ($\alpha = .05$) with results expressed as Kaplan-Meier plots. The Mantel-Haenszel χ^2 test ($\alpha = .05$) was used to compare differences in toxicity between treatment groups. Analyses of efficacy and safety included all randomly assigned and treated patients with FL and followed the intent-to-treat principle (ie, all patients included were analyzed according to their randomly assigned treatment). Statistical analyses were performed using SAS software (SAS Institute, Cary, NC). Patients will continue to be observed to obtain progression and survival information up to 4 years after the last patient has completed the last treatment cycle.

RESULTS

This open-label study was conducted at 34 active centers in Germany. A total of 358 patients were randomly assigned (177 patients assigned to MCP and 181 patients assigned to R-MCP) on the study between October 1998 and September 2003. The primary analysis population consisted of a total of 201 patients with confirmed FL (MCP, n = 96; R-MCP, n = 105; Figs 1 and 2).

Baseline Characteristics

Baseline demographic, clinical, and pathologic characteristics of the FL population were well balanced across treatment groups with the exception of sex (Table 1). The Follicular Lymphoma International Prognostic Index was applied retrospectively, and the vast majority of patients (94% in the MCP group and 92% in the R-MCP group) had intermediate- or high-risk disease according to the index.

Treatment

All eight cycles of therapy were administered to 88% of the FL population receiving R-MCP and 67% of the FL population receiving MCP. This difference was mainly a result of fewer premature withdrawals from study treatment as a result of treatment failure in the R-MCP arm; treatment failures caused by PD after two cycles occurred in three R-MCP patients and 10 MCP patients, and failure to achieve at least PR after six cycles occurred in seven R-MCP patients and 22 MCP patients. Mean doses of study drug administered were as follows: rituximab, 660 to 680 mg/cycle; mitoxantrone, 24 to 28 mg/cycle; chlorambucil, 68 to 81 mg/cycle; and prednisolone, 226 to 231 mg/cycle. Dose-intensity of the chemotherapy did not differ between treatment arms. Interferon alfa maintenance treatment (3 × 4.5 MU per week until disease progression) was initiated in 97% and 92% of planned patients in the R-MCP group and MCP group, respectively. To date, the median duration of interferon maintenance treatment is 15.5 months in the R-MCP group and 9.5 months in the MCP group, with the difference being a result of earlier disease progression in the MCP group.

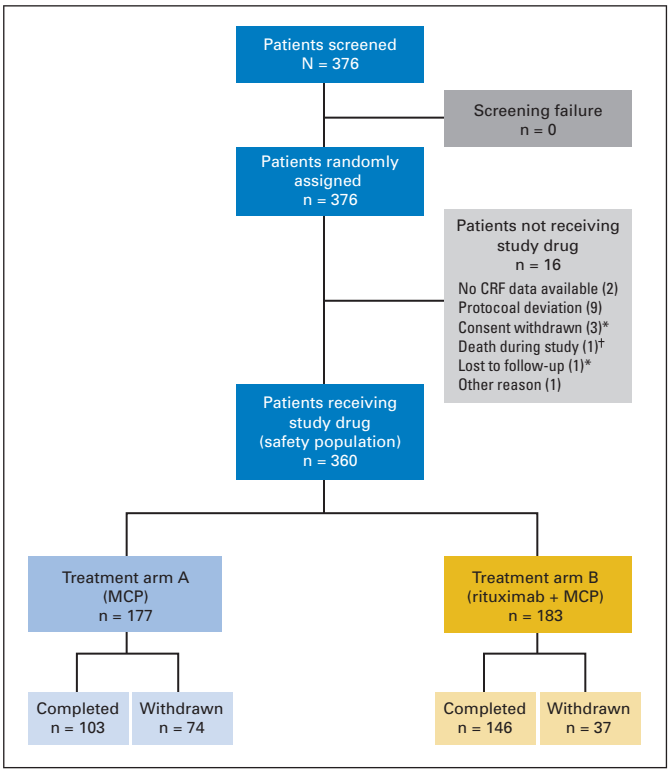

Fig 1. CONSORT diagram: overall study population. *One patient withdrew his consent and was lost to follow-up as well. †Suicide before starting treatment. Two patients started treatment with rituximab plus MCP but did not receive at least one complete therapy cycle. Therefore, the intent-to-treat population encompassed 358 patients (177 patients in the MCP group and 181 patients in the rituximab plus MCP group). Withdrawn means did not respond to treatment with complete or partial remission. CRF, case report form; MCP, mitoxantrone, chlorambucil, and prednisolone.

Efficacy

Investigators assessed remission rates (CR and PR) according to the criteria outlined in the study protocol. At the end of therapy, 92% of the FL patients treated with R-MCP were in remission (50% CR rate) compared with 75% of patients in the MCP arm (25% CR rate). Both overall remission and CR rates for R-MCP were significantly superior to those for MCP ($P = .0009$ and $P = .0004$, respectively; Table 2).

Median follow-up time for FL patients is now 47 months (R-MCP, 49 months; MCP, 42 months). In the PFS analysis, 30 events have occurred in the R-MCP group, and 50 events have occurred in

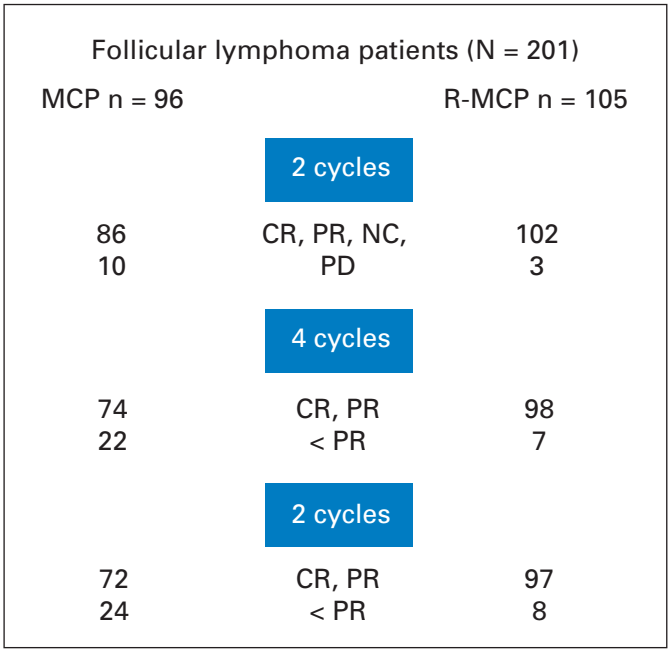

Fig 2. Outcome according to treatment group and cycle of treatment in patients with follicular lymphoma. MCP, mitoxantrone, chlorambucil, and prednisolone; R-MCP, rituximab plus mitoxantrone, chlorambucil, and prednisoline; CR, complete remission, PR, partial remission, NC, no change; PD, progressive disease.

the MCP group. The administration of R-MCP significantly prolonged PFS compared with MCP (median PFS, not reached *v* 28.8 months, respectively; $P < .0001$; Fig 3; Table 2). In the analysis of EFS, 34 patients in the R-MCP group and 57 patients in the MCP group have experienced a treatment failure event. Treatment with R-MCP significantly lengthened EFS compared with treatment with MCP (median EFS, not reached *v* 26 months, respectively; $P < .0001$; Table 2). In the analysis of OS, there have been 15 deaths in the R-MCP arm and 25 deaths in the MCP arm. Median OS time has not been reached in either treatment group, with 4-year OS rates being 87% for R-MCP and 74% for MCP ($P = .0096$; Fig 4; Table 2). During the study period and follow-up, there were 24 cause-specific deaths in the FL patient population (seven in the R-MCP arm and 17 in the MCP arm; $P = .0159$).

Adverse Events

Adverse events were reported more frequently in the R-MCP arm than in the MCP arm (99% *v* 86% of patients, respectively). As expected, the most common adverse events observed were related to the blood and bone marrow (Table 3). Seventy-two percent of patients in the R-MCP group versus 58% of patients in the MCP group experienced grade 3 or 4 leukopenia. Infections of grade 3 or 4 were observed in 8% of the MCP group and 7% of the R-MCP group. No cases of secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) have been recorded so far.

DISCUSSION

The results of this randomized trial demonstrate that the addition of rituximab to the MCP chemotherapy regimen in patients with previously untreated FL leads to highly significantly improved remission rates and a doubling of the CR rate compared with MCP chemotherapy alone. This is particularly impressive since unconfirmed CR[20] was regarded as PR only. After a median follow-up period of 47 months, this excellent remission rate translated into significantly improved

Table 1. Baseline Characteristics of the Intent-to-Treat Population of Patients With Follicular Lymphoma

Characteristic	MCP (n = 96) No. of Patients	MCP (n = 96) %*	R-MCP (n = 105) No. of Patients	R-MCP (n = 105) %*
Age, years				
Median	57		60	
Range	31-75		33-78	
Sex, male	36	37	53	50
Ann Arbor stage				
III	22	23	30	29
IV	74	77	75	71
ECOG performance status				
0	54	56	68	65
1	36	38	29	28
2	6	6	7	7
LDH > normal	30	31	31	30
Bone marrow infiltration	71	74	73	70
B symptoms				
Nightly sweating	34	35	46	44
Fever > 38°C	2	2	4	4
Body weight loss†	20	21	16	15
Follicular Lymphoma International Prognostic Index scores				
Low	6	6	8	8
Intermediate	37	39	38	36
High	53	55	59	56

Abbreviations: MCP, mitoxantrone, chlorambucil, and prednisolone; R-MCP, rituximab plus mitoxantrone, chlorambucil, and prednisolone; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.
*Percentages based on the intent-to-treat population.
†Loss of > 10% body weight within 6 months.

Table 2. Results of an Intent-to-Treat Analysis of End Points for Patients With Follicular Lymphoma

End Point	MCP (n = 96)	R-MCP (n = 105)	*P*
Tumor responses			
Complete remission			.0004
No. of patients	24	52	
%*	25	50	
Complete plus partial remission			.0009
No. of patients	72	97	
%*	75	92	
Median progression-free survival time, months	28.8	NR	< .0001
4-year overall survival rate, %	74	87	.0096
Median event-free survival time, months	26	NR	< .0001
Median response duration, months	35	NR	< .0001
Median time to next treatment, months	29.4	NR	.0002

Abbreviations: MCP, mitoxantrone, chlorambucil, and prednisolone; R-MCP, rituximab plus mitoxantrone, chlorambucil, and prednisolone; NR, not reached.
*Percentages based on the intent-to-treat population.

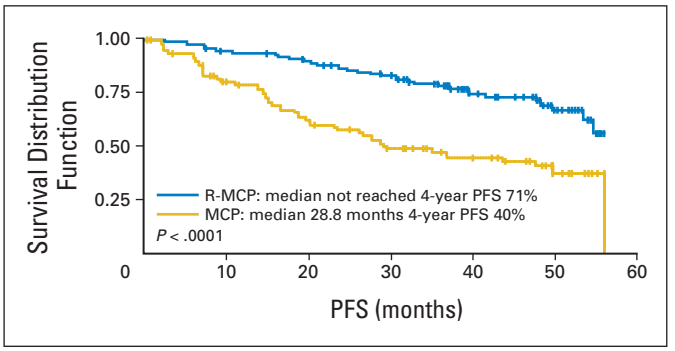

Fig 3. Progression-free survival (PFS) time for 201 follicular lymphoma patients assigned to chemotherapy with either mitoxantrone, chlorambucil, and prednisolone (MCP) or MCP plus rituximab (R-MCP).

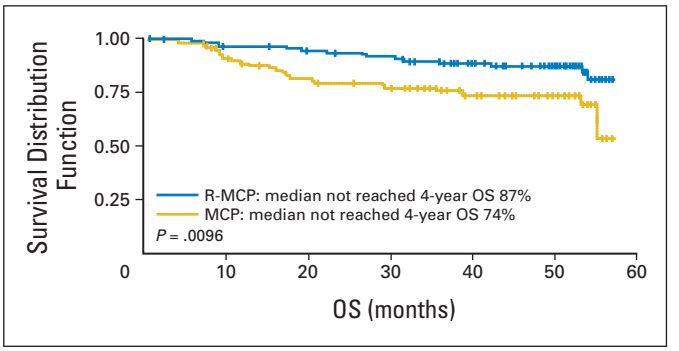

Fig 4. Overall survival (OS) time for 201 follicular lymphoma patients assigned to chemotherapy with either mitoxantrone, chlorambucil, and prednisolone (MCP) or MCP plus rituximab (R-MCP).

time to event variables for patients receiving R-MCP. Most important, the OS of patients treated with R-MCP chemotherapy was significantly prolonged (4-year OS rate, 87% for R-MCP *v* 74% for MCP; median OS time, not yet reached in both groups; $P = .0096$).

R-MCP is a well-tolerated regimen, with a pattern of adverse events similar to that seen with MCP alone. Although more patients receiving R-MCP had grade 3 or 4 leukopenia compared with patients treated with MCP, this did not translate into an increased rate of infections. To date, no patients in either treatment group have developed treatment-related MDS or AML. However, patients must be carefully observed because treatment with alkylating agents such as chlorambucil is known to increase the risk of MDS or AML,[21] and mitoxantrone may augment this effect.[22]

The combination of prednimustine, an ester of chlorambucil and prednisolone, and mitoxantrone was first introduced into NHL therapy in the 1980s.[23,24] A subsequent randomized trial in patients with indolent NHL and MCL demonstrated that prednimustine plus mitoxantrone treatment resulted in a significantly higher CR rate and event-free interval with less nonhematologic toxicity compared with cyclophosphamide, vincristine, and prednisone chemotherapy.[25] Subsequent trials in indolent NHL have shown MCP to be an effective, well-tolerated regimen.[15,16] We have shown here that the addition of rituximab to this regimen significantly improves the survival of patients with previously untreated FL, with no clinically significant increase in toxicity.

The addition of rituximab to other chemotherapy regimens has also been shown to improve clinical outcome without increasing toxicity. In a recent trial comparing eight cycles of cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy with rituximab plus CVP as first-line treatment for patients with FL, patients receiving rituximab plus CVP achieved highly significantly improved response rates, time to treatment failure, time to progression, and OS compared with patients receiving CVP (4-year OS rate, 83% *v* 77%, respectively; $P = .029$).[26,27]

The addition of rituximab has also been shown to significantly improve response rates and long-term outcomes for patients receiving

Table 3. Adverse Events According to NCIC-CTC Grading System Occurring in ≥ 10% of Follicular Lymphoma Patients Treated With MCP or R-MCP: Intent-to-Treat Analysis

	MCP (n = 96)								R-MCP (n = 105)							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
WBC	3	3	5	5	21	22	35	36	0	0	3	3	25	24	50	48
Infection	12	12	22	23	7	7	1	1	20	19	24	23	6	6	1	1
Platelets	13	14	19	20	6	6	1	1	11	10	20	19	4	4	0	0
Nausea	9	9	5	5	6	6	0	0	20	19	5	5	1	1	0	0
Hemoglobin	11	12	7	7	3	3	1	1	10	10	8	8	2	2	1	1
Rash	0	0	1	1	2	2	0	0	7	7	9	9	0	0	0	0
Heartburn	2	2	1	1	0	0	0	0	5	5	10	10	1	1	0	0
Insomnia	4	4	3	3	0	0	0	0	12	11	3	3	0	0	0	0
Diarrhea	3	3	1	1	0	0	2	2	7	7	4	4	2	2	0	0
Stomatitis	2	2	5	5	1	1	0	0	7	7	4	4	1	1	0	0
Bone pain	5	5	5	5	0	0	0	0	4	4	6	6	2	2	0	0
GI	1	1	4	4	1	1	1	1	5	5	4	4	2	2	0	0
Other	4	4	4	4	1	1	1	1	7	7	4	4	0	0	0	0

Abbreviations: NCIC-CTC, National Cancer Institute of Canada Common Toxicity Criteria; MCP, mitoxantrone, chlorambucil, and prednisolone; R-MCP, rituximab plus mitoxantrone, chlorambucil, and prednisolone.
*Number of patients reporting each event.

six to eight cycles of CHOP (as described earlier)[14] or six cycles of cyclophosphamide, doxorubicin, etoposide, and prednisone plus interferon alfa as first-line treatment for FL.[28] It is interesting to note that combining rituximab with cyclophosphamide, doxorubicin, etoposide, and prednisone and interferon alfa led to high rates of complete response (complete response/unconfirmed complete response rate at 6 months, 76% with rituximab *v* 49% in the control arm; $P < .0001$). It is possible that rituximab and interferon have a synergistic effect, leading to improvements in the quality and duration of response when the two biologic agents are used together with chemotherapy. Maintenance therapy with interferon[14,29] or rituximab[30-33] after successful induction may prolong duration of response both in previously untreated or relapsed FL patients. The R-MCP regimen should become a new standard treatment for all patients with previously untreated advanced FL requiring therapeutic intervention.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).