ORIGINAL ARTICLE

Treatment of Older Patients with Mantle-Cell Lymphoma

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ABSTRACT

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BACKGROUND

The long-term prognosis for older patients with mantle-cell lymphoma is poor. Chemoimmunotherapy results in low rates of complete remission, and most patients have a relapse. We investigated whether a fludarabine-containing induction regimen improved the complete-remission rate and whether maintenance therapy with rituximab prolonged remission.

METHODS

We randomly assigned patients 60 years of age or older with mantle-cell lymphoma, stage II to IV, who were not eligible for high-dose therapy to six cycles of rituximab, fludarabine, and cyclophosphamide (R-FC) every 28 days or to eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 21 days. Patients who had a response underwent a second randomization to maintenance therapy with rituximab or interferon alfa, each given until progression.

RESULTS

Of the 560 patients enrolled, 532 were included in the intention-to-treat analysis for response, and 485 in the primary analysis for response. The median age was 70 years. Although complete-remission rates were similar with R-FC and R-CHOP (40% and 34%, respectively; P=0.10), progressive disease was more frequent with R-FC (14%, vs. 5% with R-CHOP). Overall survival was significantly shorter with R-FC than with R-CHOP (4-year survival rate, 47% vs. 62%; P=0.005), and more patients in the R-FC group died during the first remission (10% vs. 4%). Hematologic toxic effects occurred more frequently in the R-FC group than in the R-CHOP group, but the frequency of grade 3 or 4 infections was balanced (17% and 14%, respectively). In 274 of the 316 patients who were randomly assigned to maintenance therapy, rituximab reduced the risk of progression or death by 45% (in remission after 4 years, 58%, vs. 29% with interferon alfa; hazard ratio for progression or death, 0.55; 95% confidence interval, 0.36 to 0.87; P=0.01). Among patients who had a response to R-CHOP, maintenance therapy with rituximab significantly improved overall survival (4-year survival rate, 87%, vs. 63% with interferon alfa; P=0.005).

CONCLUSIONS

R-CHOP induction followed by maintenance therapy with rituximab is effective for older patients with mantle-cell lymphoma. (Funded by the European Commission and others; ClinicalTrials.gov number, NCT00209209.)

PATIENTS WITH MANTLE-CELL LYMPHOMA typically present with extensive disease and involvement of multiple lymph nodes as well as the spleen, bone marrow, blood, and gastrointestinal tract. The median age at diagnosis is about 65 years.[1,2] Standard therapy for these patients consists of chemotherapy (e.g., the CHOP regimen, consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone) combined with the anti-CD20 monoclonal antibody rituximab (e.g., R-CHOP).[2-4] Only a minority of patients have a complete remission, and relapse or progression usually occurs within 2 to 3 years, resulting in an overall survival of less than 5 years.

To improve this grim prognosis, we attempted to establish a more effective induction therapy, resulting in an increased rate of complete remission, and better postinduction strategies, such as maintenance therapy, that would prolong the duration of remission. Several previous studies have investigated fludarabine-containing regimens, which showed high efficacy in follicular lymphoma and relapsed mantle-cell lymphoma.[4-7] A trial of a combination of fludarabine, cyclophosphamide with or without mitoxantrone, and rituximab showed promising results.[8] Considering the risk of cardiac toxic effects in older patients, treatments that excluded anthracyclines were particularly attractive.

Maintenance therapy with interferon alfa showed a tendency toward prolongation of progression-free survival in patients with mantle-cell lymphoma and was therefore considered standard therapy in a previous trial.[9] Maintenance therapy with rituximab had significantly improved the duration of response in patients with relapsed follicular lymphoma or mantle-cell lymphoma[10] and seemed to be a promising alternative, given the strong CD20 expression on mantle-cell-lymphoma cells.

Therefore, in 2004, we initiated a double-randomized intergroup trial with two objectives. First, we compared the rates of response to an induction regimen consisting of fludarabine, cyclophosphamide, and rituximab (R-FC) and an induction regimen with R-CHOP. Second, we studied the duration of remission; patients who had a response were randomly assigned to maintenance therapy with rituximab or interferon alfa (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

METHODS

CHARACTERISTICS OF THE PATIENTS

Eligible patients had newly diagnosed, histologically confirmed mantle-cell lymphoma,[1] Ann Arbor stage II to IV; were 66 years of age or older or were 60 to 65 years of age if they were ineligible for high-dose treatment; and had an Eastern Cooperative Oncology Group performance status of 2 or less (with 0 indicating asymptomatic, 1 symptomatic but ambulatory, and 2 symptomatic and in bed less than half the day). Pathological findings were centrally reviewed by the Pathology Panel of the European Mantle Cell Lymphoma Network.[11] Patients were excluded if they had a leukocyte count of less than 2×10^9 per liter, a platelet count of less than 100×10^9 per liter, a liver-enzyme level greater than 3 times the upper limit of the normal range, a bilirubin level greater than 2.5 times the upper limit of the normal range, or a creatinine level greater than 2 times the upper limit of the normal range, if these counts or levels were unrelated to mantle-cell lymphoma. Additional exclusion criteria were involvement of the central nervous system, a history of autoimmune cytopenia, hypersensitivity to murine antibodies, other cancers, and serious cardiac, pulmonary, neurologic, or endocrine disease or other conditions that might interfere with adherence to the study.

STUDY PROTOCOL

The study was performed in accordance with the updated Declaration of Helsinki, and all patients provided written informed consent. Both randomizations were performed centrally at the data center of the European Mantle Cell Lymphoma Network or at the data center of the Hemato-Oncology Foundation for Adults in the Netherlands (HOVON) and were stratified according to study group, age, and the International Prognostic Index[12] risk profile. The second randomization was also stratified according to the induction regimen and the category of response. On behalf of the European Mantle Cell Lymphoma Network, the first, second, penultimate, and last authors designed the study and vouch for the accuracy and completeness of the data and analysis and the fidelity of the study to the protocol; these authors wrote the manuscript and made the decision to submit it for publication. The second and penultimate authors gathered and analyzed the data.

Roche Pharmaceuticals and Schering-Plough supplied maintenance medication at no cost but played no role in the design or execution of the study, the data collection or analysis, or the writing of the manuscript. The protocol, including the statistical analysis plan, is available at NEJM.org.

INDUCTION TREATMENT

Induction therapy consisted of either R-FC or R-CHOP open-label chemoimmunotherapy. Rituximab was added to the chemotherapy when the count of circulating lymphoma cells was less than 10×10^9 per liter. The R-FC regimen consisted of rituximab at a dose of 375 mg per square meter of body-surface area given intravenously on day 1 (maximum dose, 750 mg), fludarabine at a dose of 30 mg per square meter given intravenously on days 1 through 3, and cyclophosphamide at a dose of 250 mg per square meter given intravenously on days 1 through 3. The regimen was repeated at day 29 for six cycles. The R-CHOP regimen consisted of rituximab at a dose of 375 mg per square meter (maximum dose, 750 mg), cyclophosphamide at a dose of 750 mg per square meter, doxorubicin at a dose of 50 mg per square meter, and vincristine at a dose of 1.4 mg per square meter (maximum dose, 2 mg), all given intravenously on day 1, and oral prednisone at a dose of 100 mg given on days 1 through 5. The regimen was repeated at day 22 for eight cycles. If neurologic toxic effects occurred, the dose of vincristine was modified at the physician's discretion.

Subsequent courses were postponed for 1 week if the leukocyte count was less than 4×10^9 per liter or the platelet count was less than 100×10^9 per liter. Doses of fludarabine, cyclophosphamide, and doxorubicin in subsequent cycles were modified if myelosuppression was persistent (see the Supplementary Appendix). If progression occurred, induction was stopped.

MAINTENANCE TREATMENT

The option to participate in the second randomization was offered to patients who had a response to the induction regimen, a leukocyte count greater than 3×10^9 per liter, and a platelet count greater than 100×10^9 per liter (or greater than 75×10^9 per liter, according to a protocol amendment in 2009). Open-label maintenance therapy started immediately after the date of the second randomization

and continued until progression. Rituximab was continued at a dose of 375 mg per square meter every 2 months. Standard interferon alfa was administered subcutaneously at a dose of 3 million units three times per week; pegylated interferon alfa was administered at a dose of 1 μg per kilogram of body weight per week. If any toxic effect of grade 2 or 3 occurred, the dose was reduced by 30 to 50%; for any toxic effect of grade 4, treatment with interferon alfa was interrupted until recovery, then resumed at 50% of the previous dose, and gradually increased if serious adverse events did not occur.

STAGING PROCEDURES, RESPONSE MONITORING, AND END POINTS

Baseline measurements consisted of computed tomography (CT) of the neck, chest, abdomen, and pelvis, and a trephine biopsy of bone marrow; additional investigations were performed if clinically indicated. The response was evaluated according to the 1999 consensus criteria[13] (see the Supplementary Appendix). CT studies and testing for other initially positive findings were repeated at midterm (i.e., after four cycles of R-CHOP or three cycles of R-FC) and at the end of the induction phase. The response to induction chemotherapy was determined 4 weeks after the last cycle. During follow-up, response evaluations were performed twice yearly until progression.

The primary prespecified end point for the comparison of the induction regimens was the rate of complete remission (excluding unconfirmed complete remissions). For the primary analysis, the response was classified as a premature stop if the induction regimen was stopped either earlier than midterm, in patients without progression, or when less than two thirds of the cycles had been completed, in patients who had a response. The primary prespecified end point for the comparison of maintenance regimens was the duration of remission, which was calculated as the interval from the last day of induction therapy until progression or death from any cause. The secondary end points were the overall response rate, the time to treatment failure (defined as stable disease, relapse, progression, or death) from the start of induction therapy, overall survival, and toxic effects.

STATISTICAL ANALYSIS

The overall response rate and the duration of remission were monitored by sequential analyses[14] with planned interim analyses. The study was designed to have 95% power to detect an increase in the rate of complete remission from 50% after R-CHOP to 65% after R-FC, at a one-sided significance level of 5%. For the duration of remission, the study was designed to have 95% power to detect a 40% reduction in the risk of progression or death with rituximab, as compared with interferon alfa, at a two-sided significance level of 5%. We calculated that we would need to enroll a total of 570 patients (allowing for withdrawals from the study), and that a maximum of 240 events, with adjustment for the sequential design (Fig. S2A in the Supplementary Appendix), would be needed to compare the duration of remission with the two maintenance regimens.

As prespecified in the protocol, the primary analysis included patients with mantle-cell lymphoma of stage II to IV who underwent randomization and had started treatment in accordance with the randomization result; data for patients receiving maintenance therapy who started another antilymphoma therapy without progression were censored at the time of the protocol violation. All secondary efficacy analyses were performed according to the intention-to-treat principle, with all patients who underwent randomization included and protocol violations ignored. For safety analyses, patients were evaluated as treated.

Remission rates and other categorical variables were compared by means of Fisher's exact test; time-to-event variables were described with the use of Kaplan–Meier estimates and compared with use of the log-rank test. P values for sequentially monitored end points were reported with adjustment for interim analyses. For the maintenance-therapy comparison, a potential interacting effect by type of induction therapy was explored by means of multiple Cox regression. In the case of a significant interaction, stratified effects were reported. The calculation of the sample size and the sequential monitoring were performed with the use of PEST software, version 3 (Applied Statistics Department, University of Reading, Reading, United Kingdom). Statistical analysis was performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

INDUCTION TREATMENT

Between January 2004 and October 2010, a total of 560 patients from eight countries were randomly assigned to chemotherapy with R-CHOP or R-FC; 532 of these patients were included in the intention-to-treat analysis and 485 were included in the primary analysis (Fig. 1A). Table 1 and Table S1 in the Supplementary Appendix show the demographic and clinical characteristics of the patients.

The rate of complete remissions at the end of induction therapy was not significantly higher after R-FC (98 of 246 patients [40%]) than after R-CHOP (81 of 239 [34%]) (P=0.10 with a one-sided test, in the primary analysis). The overall response rate was lower after R-FC than after R-CHOP but the difference was not significant (192 of 246 patients [78%] and 206 of 239 [86%], respectively; P=0.06, with adjustment for interim analyses), and complete-remission rates, including unconfirmed complete remission, were also similar (53% and 49%, respectively). The rate of progression was higher during R-FC than during R-CHOP (14% vs. 5%). The intention-to-treat analysis yielded identical results (Table S2 in the Supplementary Appendix). After a median follow-up of 37 months, the time to treatment failure was similar with R-FC and R-CHOP (median, 26 and 28 months, respectively) (Fig. 2A) with a similar duration of remission (37 and 36 months, respectively).

However, the overall survival was significantly shorter after R-FC than after R-CHOP (survival rate at 4 years, 47% vs. 62%; P=0.005; hazard ratio for death, 1.50; 95% confidence interval [CI], 1.13 to 1.99) (Fig. 2B). Of the 560 patients, 199 died — 115 of 280 patients in the R-FC group and 84 of 280 in the R-CHOP group. Causes of death were mainly related to progression of lymphoma (64 patients in the R-FC group vs. 47 in the R-CHOP group). In addition, more patients who received R-FC died from infection, as compared with those who received R-CHOP (19 vs. 12), or from a secondary cancer (9 vs. 3). The remaining causes of death in the R-FC and R-CHOP groups, respectively, were related to cardiac causes (4 and 9 patients), pulmonary causes (3 and 2), central nervous system bleeding or ischemia (2 and 1), leukoencephalopathy (1 and 1), or unknown

A

560 Patients underwent randomization

280 Were assigned to R-CHOP

280 Were assigned to R-FC

6 Did not start treatment
3 Withdrew consent
1 Was lost to follow-up
2 Did not have MCL

3 Did not start treatment
1 Withdrew consent
1 Did not have acceptable medical center
1 Did not have MCL

274 Started treatment
273 Received R-CHOP
1 Received rituximab

277 Started treatment
277 Received R-FC

7 Had undocumented responses
7 Were not staged for response, including 1 who received rituximab

12 Had undocumented responses
1 Was lost to follow-up
11 Were not staged for response

267 Were included in the intention-to-treat analysis

265 Were included in the intention-to-treat analysis

28 Were excluded
13 Did not have MCL
1 Had stage I MCL
14 Stopped treatment early

19 Were excluded
4 Did not have MCL
1 Had stage I MCL
14 Stopped treatment early

239 Were included in the primary analysis

246 Were included in the primary analysis

B

560 Patients underwent randomization for induction therapy

244 Did not undergo the second randomization
93 Were not in remission
44 Stopped induction therapy prematurely
29 Had persistent cytopenia
8 Had contraindications
16 Withdrew or were withdrawn by physician
2 Had other reasons
17 Had unknown reasons
35 Were advised to start rituximab after closure of randomization

316 Underwent randomization for maintenance therapy

30 Were excluded
23 Did not start maintenance therapy
9 Had cytopenia
8 after R-FC
1 after R-CHOP
2 Were lost to follow-up
4 Withdrew
2 Had contraindications
2 Had other reasons
4 Had unknown reasons
2 Did not have MCL
1 Had stage I MCL
4 Started rituximab

161 Were assigned to interferon alfa

155 Were assigned to rituximab

12 Were excluded
8 Did not start maintenance therapy
5 Had cytopenia after R-FC
2 Were lost to follow-up
1 Had unknown reason
4 Did not have MCL

131 Were included in the primary analysis

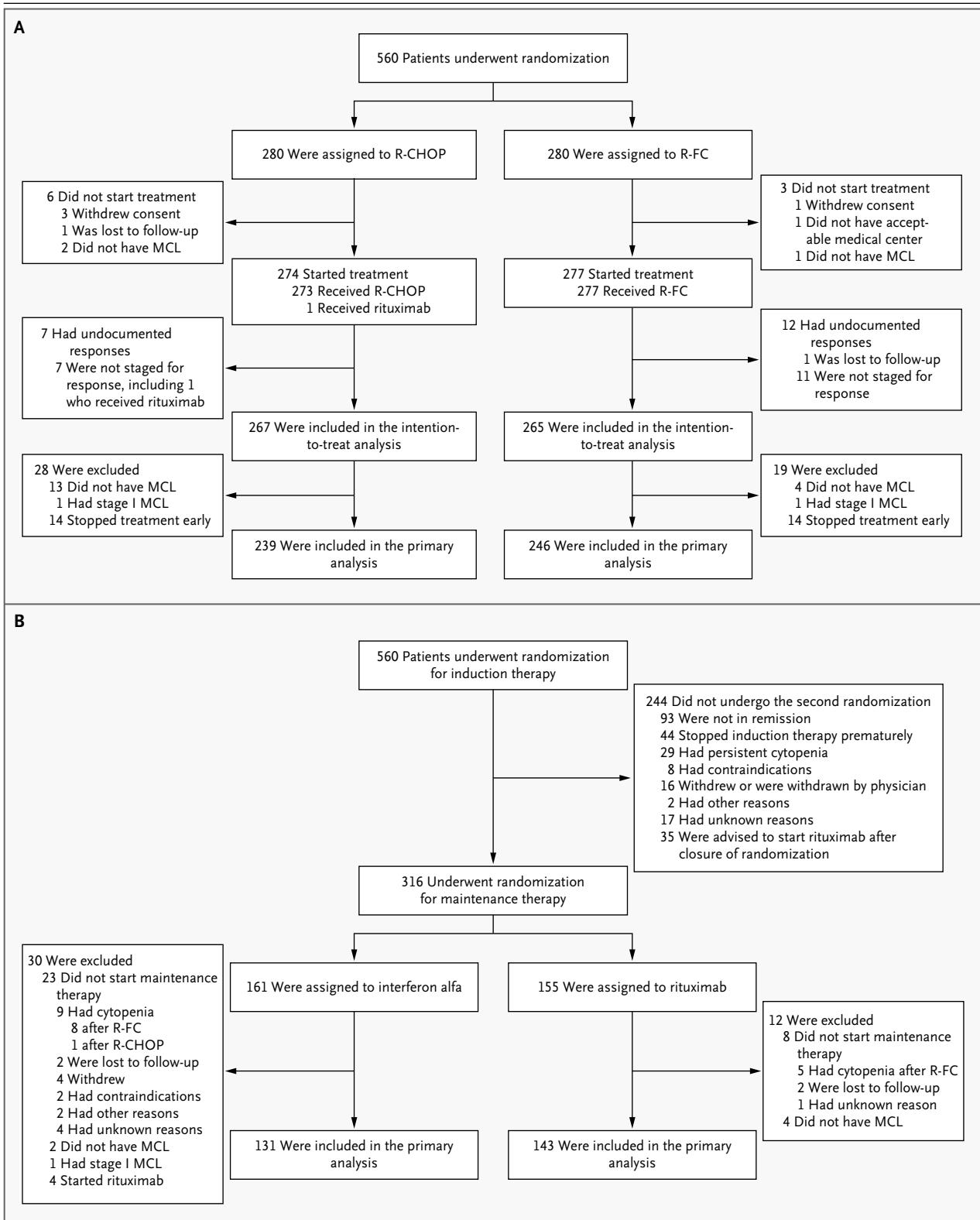143 Were included in the primary analysis

Figure 1 (facing page). Randomization and Inclusion in the Intention-to-Treat and Primary-Analysis Populations for Induction and Maintenance Therapy.

Panel A shows the first randomization phase, for induction therapy. Panel B shows the second randomization phase, for maintenance therapy. Details regarding reasons for exclusion are provided in Figure 1A in the Supplementary Appendix. Patients who stopped treatment early ("premature stop," defined as discontinuation of the induction therapy before the midterm point in the absence of progression or discontinuation after less than two thirds of the cycles had been completed in patients with a response) were included in the intention-to-treat analysis but were not included in the primary analysis. MCL denotes mantle-cell lymphoma; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and R-FC rituximab, fludarabine, and cyclophosphamide.

causes (13 and 9). Notably, 29 patients (10%) who received R-FC died while in remission, as compared with 11 (4%) who received R-CHOP. Owing to the observed difference in overall survival, the independent data and safety monitoring committee recommended closing the R-FC group.

Hematologic toxic effects occurred more frequently in the R-FC group than in the R-CHOP group (Table 2). Grade 1 or 2 constipation and neuropathy were more frequent among patients who received R-CHOP than among those who received R-FC. Grade 3 or 4 infections were balanced between the R-FC and R-CHOP groups, occurring in 17% and 14% of patients, respectively, but there was a trend toward a higher frequency of febrile neutropenia among patients who received R-CHOP than among those who received R-FC (17% vs. 11%, P=0.052). Cardiac toxic effects of grade 3 or 4 were uncommon, occurring in 3 to 4% of all patients, and the rates were similar in the two groups.

Owing to higher rates of hematologic toxic effects, treatment compliance was worse among patients who received R-FC: 23% of these patients who had a response did not complete all cycles, as compared with 12% of those who received R-CHOP and had a response. The median duration of induction therapy in the R-FC group was 143 days (interquartile range, 106 to 161), as expected, with a median average cycle duration of 31 days; the median duration of induction therapy in the R-CHOP group was 152 days (interquartile range,

147 to 163), as expected, with a median average cycle duration of 21 days.

MAINTENANCE TREATMENT

A total of 316 patients were randomly assigned to rituximab or interferon alfa, of whom 274 were included in the primary analysis (143 in the rituximab group and 131 in the interferon alfa group). The characteristics of the patients and reasons for not undergoing randomization or evaluation are shown in Figure 1B and Table 1 and in Table S1 in the Supplementary Appendix. Persistent cytopenia in 29 patients who had received R-FC precluded participation in the second randomization, because maintenance therapy with interferon alfa required adequate hematopoietic function. For the primary analysis, censoring due to protocol violation occurred in eight cases, all in the group that received interferon alfa; 6 patients switched to maintenance therapy with rituximab, 1 to the combination of rituximab and interferon alfa, and 1 to radiotherapy. The median follow-up for assessment of the duration of remission was 36 months (37 months in the rituximab group and 34 months in the interferon alfa group).

The remission duration was significantly longer in the rituximab group than in the interferon alfa group, with a 45% reduction in the risk of progression or death according to the primary analysis (hazard ratio, 0.55; 95% CI, 0.36 to 0.87; P=0.01, with adjustment for interim analyses) (Fig. S2B in the Supplementary Appendix). At 4 years, 58% of the patients who received rituximab were still in remission (50 events) versus 29% of those who received interferon alfa (71 events). The same effect was seen in the intention-to-treat analysis, with a 4-year rate of 57% in the rituximab group versus 34% in the interferon alfa group (Fig. 3A). Multivariable regression showed significantly different effects of rituximab according to the induction regimen (P=0.04) (Table S3 in the Supplementary Appendix). The influence of maintenance therapy with rituximab on the duration of remission was detected in patients who received R-CHOP but not in those who received R-FC (Fig. 3B, and Fig. S3A in the Supplementary Appendix).

The overall survival did not differ significantly between the maintenance groups: survival rates at 4 years were 79% in the rituximab group and 67% in the interferon alfa group (P=0.13) (Fig. 3C).

Table 1. Baseline Characteristics of the Patients Included in the Primary Analysis.*

Characteristic	Induction Phase			Maintenance Phase		
	Total (N = 485)	R-FC (N = 246)	R-CHOP (N = 239)	Total (N = 274)	Rituximab (N = 143)	Interferon Alfa (N = 131)
Age — yr						
Median	70	70	70	70	69	71
Range	60–87	60–83	61–87	60–83	60–81	60–83
Male sex — no. (%)	340 (70)	178 (72)	162 (68)	193 (70)	98 (69)	95 (73)
Ann Arbor stage — no. (%)						
II	30 (6)	18 (7)	12 (5)	17 (6)	7 (5)	10 (8)
III	55 (11)	30 (12)	25 (10)	34 (12)	17 (12)	17 (13)
IV	400 (82)	198 (80)	202 (85)	223 (81)	119 (83)	104 (79)
Systemic symptom — no. (%)†	182 (38)	93 (38)	89 (37)	103 (38)	57 (40)	46 (35)
ECOG performance status of 2 — no. (%)‡	39 (8)	21 (9)	18 (8)	13 (5)	3 (2)	10 (8)
Bone-marrow involvement — no. (%)	364 (75)	182 (74)	182 (76)	202 (74)	104 (73)	98 (75)
LDH elevation — no. (%)	206 (42)	104 (42)	102 (43)	99 (36)	55 (38)	44 (34)
Median ratio of LDH activity to ULN	0.94	0.93	0.95	0.89	0.90	0.89
Median leukocyte count — ×10^{-9}/liter	7.8	7.7	7.9	7.5	7.6	7.1
MIPI§						
Median score	6.20	6.20	6.18	6.13	6.15	6.13
Low risk — no. (%)	42 (9)	24 (10)	18 (8)	26 (9)	13 (9)	13 (10)
Intermediate risk — no. (%)	201 (41)	98 (40)	103 (43)	129 (47)	64 (45)	65 (50)
High risk — no. (%)	242 (50)	124 (50)	118 (49)	119 (43)	66 (46)	53 (40)
Received R-CHOP — no. (%)	NA	NA	NA	163 (59)	82 (57)	81 (62)
Complete remission, excluding unconfirmed — no. (%)	NA	NA	NA	119 (43)	70 (49)	49 (37)
Complete remission, including unconfirmed — no. (%)	NA	NA	NA	167 (61)	89 (62)	78 (60)

* P>0.05 for all comparisons. All variables were evaluated before the start of induction therapy. LDH denotes lactate dehydrogenase; NA not applicable; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-FC rituximab, fludarabine, and cyclophosphamide; and ULN upper limit of the normal range.
† Systemic symptoms were defined as B symptoms in the Ann Arbor classification.
‡ Scores on the Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with 0 indicating asymptomatic, 1 symptomatic but ambulatory, and 2 symptomatic and in bed less than half the day; 5 indicates death.
§ The Mantle-Cell Lymphoma International Prognostic Index[15] (MIPI) score is calculated from the individual patient characteristics of age, ECOG performance status, LDH, and leukocyte count, and its range depends on the range of these characteristics. Typical scores range from 4 to 10, with higher scores indicating higher-risk disease. The index classifies patients as having low-, intermediate-, or high-risk disease (see the Supplementary Appendix).

However, there was a significant modification of the effect of maintenance therapy according to the induction regimen (P=0.02) (Table S3 in the Supplementary Appendix), with a survival gain at 4 years among the patients who received R-CHOP (87% in the rituximab group vs. 63% in the interferon alfa group; P=0.005) (Fig. 3D) but not among the patients who received R-FC (P=0.48) (Fig. S3B in the Supplementary Appendix).
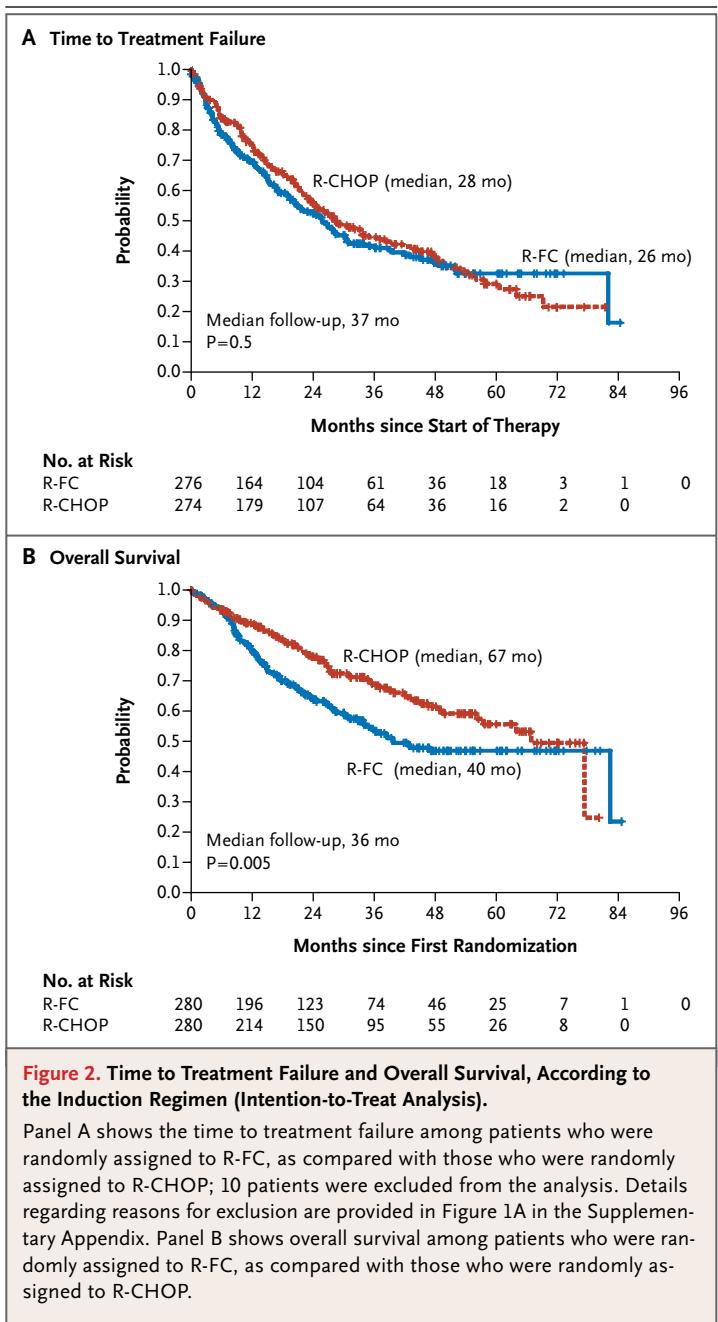
Toxic effects during the maintenance phase were more pronounced in the interferon alfa group, with more patients having leukocytopenia, thrombocytopenia, and fatigue, mostly of grade 1 or 2, whereas rituximab was associated with more grade 1 or 2 infections (Table 2). Adherence to treatment reflected these observed differences. Overall, the median duration of maintenance therapy was 25 months with rituximab versus

7 months with interferon alfa. After 1 year, maintenance therapy with interferon alfa had been stopped in 49% of patients while they were in remission, whereas after 4 years, a premature stop of maintenance therapy with rituximab had occurred in only 28% of patients. A total of 35 patients who had a response were recommended for treatment with rituximab after closure of the randomization for maintenance therapy.

DISCUSSION

This randomized trial, coordinated within the European Mantle Cell Lymphoma Network, focused on older patients with mantle-cell lymphoma. Our results show that the fludarabine-containing induction regimen was not more effective but was more toxic than R-CHOP. Maintenance therapy with rituximab almost doubled the duration of remission in patients who had a response to induction therapy and significantly improved overall survival among patients who had a response to R-CHOP.

The outcome of the fludarabine-containing regimen was disappointing, given the high expectations in the early 2000s. We powered the study to detect an absolute increase of 15 percentage points in the rate of complete remission with R-FC, assuming that more complete remissions would result in a longer duration of remission and better overall survival. The increase in early progressions was unexpected and resulted — in combination with more toxic events — in more deaths. Both the poor performance of the R-FC regimen itself and insufficient hematopoietic recovery during and after the induction phase were responsible for the fact that fewer patients who received this regimen were eligible for the maintenance phase. Similar serious toxic effects, including severe and sometimes fatal adverse events, were reported with fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia, and therefore, this regimen was not considered suitable for patients who were older than 70 years of age or who had two or more coexisting conditions.[16,17] One possible criticism of the R-FC regimen in our trial is that it provided less dose-dense rituximab than did the R-CHOP regimen: one dose every 28 days for six cycles versus one dose every 21 days for eight cycles. However, we assumed that this difference would be inconsequential.

Figure 2. Time to Treatment Failure and Overall Survival, According to the Induction Regimen (Intention-to-Treat Analysis).

Panel A shows the time to treatment failure among patients who were randomly assigned to R-FC, as compared with those who were randomly assigned to R-CHOP; 10 patients were excluded from the analysis. Details regarding reasons for exclusion are provided in Figure 1A in the Supplementary Appendix. Panel B shows overall survival among patients who were randomly assigned to R-FC, as compared with those who were randomly assigned to R-CHOP.

The excellent results with rituximab administered as maintenance therapy are important. Maintenance therapy with rituximab showed not only a progression-free survival benefit but also a significant survival advantage among patients who were successfully pretreated with R-CHOP. The protocol specification that maintenance therapy should continue until progression, which had been

based on the poor outcome of salvage treatments in patients with relapsed mantle-cell lymphoma, was followed in the majority of patients who received maintenance therapy with rituximab. One might argue that the excellent outcome of maintenance therapy with rituximab was due solely to the poor performance of interferon alfa. However, our results with interferon alfa are better than or in line with those of previous trials.[18,19] Moreover, a decrease in progression-free survival associated with interferon alfa has not been reported from any trial. Finally, we performed an intention-to-treat analysis that included the 83 patients who

had a response and who, before closure of the second randomization, were not randomly assigned to either maintenance regimen (none of whom received maintenance therapy with interferon alfa), with adjustment for risk profile as assessed with the use of Mantle-Cell Lymphoma International Prognostic Index[15] (see the Supplementary Appendix) and category of response (Fig. S4 and Table S4 in the Supplementary Appendix). The duration of remission and overall survival time after a response to R-CHOP were significantly shorter among patients who were not assigned to any maintenance therapy, as compared with those

Table 2. Toxic Events, According to Grade and Induction and Maintenance Regimens (as-Treated Analysis).*

Event	R-FC (N = 268)	R-CHOP (N = 249)	Rituximab (N = 140)	R-FC + Rituximab (N = 59)	R-CHOP + Rituximab (N = 81)	Interferon Alfa (N = 117)	R-FC + Interferon Alfa (N = 43)	R-CHOP + Interferon Alfa (N = 74)
	percentage of patients with event of maximal grade							
Anemia								
Grade 1 or 2	59	68	41	53	32	42	52	36
Grade 3 or 4	20	12†	4	5	4	4	10	0
Leukocytopenia								
Grade 1 or 2	18	29	49	46	51	50	37	58
Grade 3 or 4	73	59‡	19	39	4	33§	60	18
Lymphocytopenia								
Grade 1 or 2	9	19	33	15	46	24	12	31
Grade 3 or 4	78	69‡	45	69	27	60	81	46
Neutropenia								
Grade 1 or 2	18	20	27	27	28	29	21	34
Grade 3 or 4	69	60	24	37	15	36	64	19
Thrombocytopenia								
Grade 1 or 2	39	33	27	47	13	42	44	40
Grade 3 or 4	41	18¶	6	14	1	15§	33	4
Elevated bilirubin								
Grade 1 or 2	15	8	7	8	6	8	10	7
Grade 3 or 4	1	1†	0	0	0	0	0	0
Nausea								
Grade 1 or 2	36	26	11	17	6	15	21	11
Grade 3 or 4	2	1†	0	0	0	0	0	0
Constipation								
Grade 1 or 2	15	28	7	8	6	7	7	7
Grade 3 or 4	2	3‡	1	2	0	0	0	0

Table 2. (Continued.)

Event	R-FC (N=268)	R-CHOP (N=249)	Rituximab (N=140)	R-FC + Rituximab (N=59)	R-CHOP + Rituximab (N=81)	Interferon Alfa (N=117)	R-FC + Interferon Alfa (N=43)	R-CHOP + Interferon Alfa (N=74)
	percentage of patients with event of maximal grade							
Neuropathy								
Grade 1 or 2	7	36	14	3	23	14	7	18
Grade 3 or 4	1	4¶	1	2	0	1	0	1
Fatigue								
Grade 1 or 2	50	52	28	25	29	48	41	51
Grade 3 or 4	4	6	1	3	0	5‖	10	3
Infection								
Grade 1 or 2	18	31	31	36	27	17	21	14
Grade 3 or 4	17	14‡	9	14	5	11**	12	11
Myalgia or arthralgia								
Grade 1 or 2	9	12	14	15	13	19	12	22
Grade 3 or 4	0	3†	1	0	1	3	2	3
Febrile neutropenia††	11	17	3	5	1	4	10	1

* Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 2.0. The maximal grade is the highest grade of adverse event that a patient had during the treatment period; patients were included only in the percentage for the highest grade of event they had. The following events were associated with no significant difference between the two induction regimens or between the two maintenance regimens and were grade 3 or 4 in 0 to 8% of patients: elevated creatinine, elevated aminotransferases, vomiting, diarrhea, mucositis, decreased cardiac function, decreased pulmonary function, depression, allergy, weight loss, and bleeding.
† P<0.05 for adverse events of maximal grade 0 versus grade 1 or 2 versus grade 3 or 4 for R-FC versus R-CHOP.
‡ P<0.01 for adverse events of maximal grade 0 versus grade 1 or 2 versus grade 3 or 4 for R-FC versus R-CHOP.
§ P<0.01 for adverse events of maximal grade 0 versus grade 1 or 2 versus grade 3 or 4 for rituximab versus interferon alfa.
¶ P<0.001 for adverse events of maximal grade 0 versus grade 1 or 2 versus grade 3 or 4 for R-FC versus R-CHOP.
‖ P<0.001 for adverse events of maximal grade 0 versus grade 1 or 2 versus grade 3 or 4 for rituximab versus interferon alfa.
** P<0.05 for adverse events of maximal grade 0 versus grade 1 or 2 versus grade 3 or 4 for rituximab versus interferon alfa.
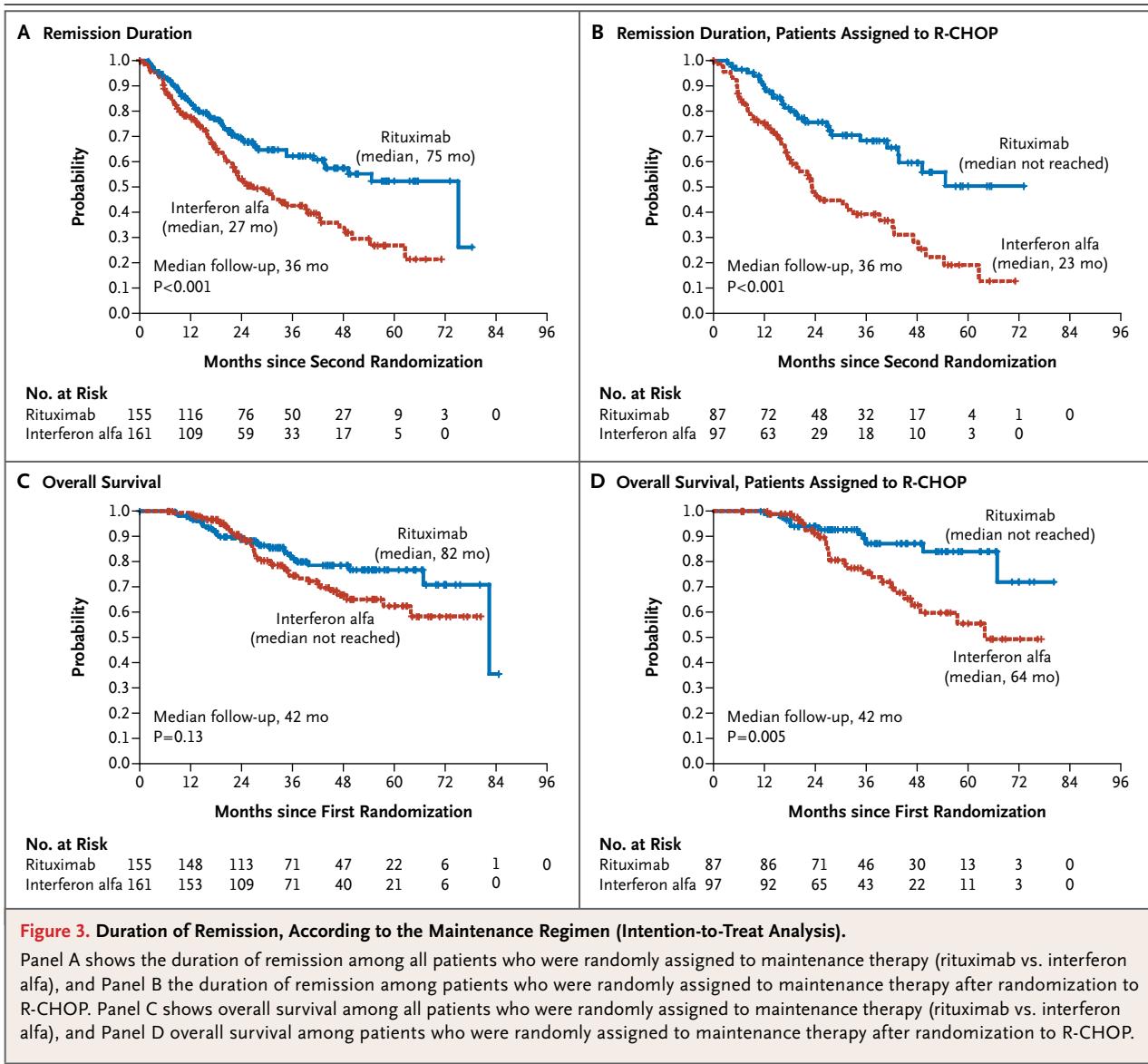†† This adverse event is graded only within the 3 and 4 categories.

who were randomly assigned to interferon alfa (P=0.002 and P<0.001, respectively). Although these data are not based on a randomized comparison, we believe that they strongly support the use of maintenance therapy with rituximab in older patients who have a response to R-CHOP.

Although our data are promising, patients still died from this lymphoma during the induction and maintenance phases. Thus far, standard first-line therapy for younger patients — consisting of high-dose cytarabine, followed by autologous stem-cell transplantation — is generally not feasible for older patients. On the other hand, cytarabine seems to be one of the most important drugs in the treatment of mantle-cell lymphoma,[2,20,21] and adapted doses appear to be feasible for older

patients with relapsed mantle-cell lymphoma.[22] Bendamustine-based treatment has been reported to be active against mantle-cell lymphoma on the basis of a subgroup analysis in a German first-line trial.[23] Thus, bendamustine-containing combinations or molecular-targeted approaches that have shown high response rates among patients with relapsed mantle-cell lymphoma might be alternative induction regimens.[22,24-26] Similarly, it may be attractive to combine the rituximab-based maintenance regimen with other drugs that have been shown to be active against mantle-cell lymphoma. However, physicians need to be aware of the potential interactions between the initial therapy and the maintenance regimen.

In conclusion, older patients with mantle-cell

Figure 3. Duration of Remission, According to the Maintenance Regimen (Intention-to-Treat Analysis).

Panel A shows the duration of remission among all patients who were randomly assigned to maintenance therapy (rituximab vs. interferon alfa), and Panel B the duration of remission among patients who were randomly assigned to maintenance therapy after randomization to R-CHOP. Panel C shows overall survival among all patients who were randomly assigned to maintenance therapy (rituximab vs. interferon alfa), and Panel D overall survival among patients who were randomly assigned to maintenance therapy after randomization to R-CHOP.

lymphoma who have a response to R-CHOP and continue to receive rituximab as maintenance therapy have a longer life expectancy than those who receive maintenance therapy with interferon alfa.

APPENDIX

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