ORIGINAL ARTICLE

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

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ABSTRACT

BACKGROUND

Mantle-cell lymphoma is generally incurable. Despite high rates of complete response after initial immunochemotherapy followed by autologous stem-cell transplantation, patients have relapses. We investigated whether rituximab maintenance therapy at a dose of 375 mg per square meter of body-surface area administered every 2 months for 3 years after transplantation would prolong the duration of response.

METHODS

In a phase 3 trial involving 299 patients who were younger than 66 years of age at diagnosis, we randomly assigned 240 patients to receive rituximab maintenance therapy or to undergo observation after autologous stem-cell transplantation (120 patients per group); 59 patients did not undergo randomization. The primary end point was event-free survival (with an event defined as disease progression, relapse, death, allergy to rituximab, or severe infection) after transplantation among patients who underwent randomization.

RESULTS

After four courses of immunochemotherapy induction (rituximab, dexamethasone, cytarabine, and a platinum derivative [R-DHAP]), the overall response rate was 89%, and the complete response rate 77%. Transplantation was performed in 257 patients. The median follow-up from randomization after transplantation was 50.2 months (range, 46.4 to 54.2). Starting from randomization, the rate of event-free survival at 4 years was 79% (95% confidence interval [CI], 70 to 86) in the rituximab group versus 61% (95% CI, 51 to 70) in the observation group (P=0.001). The rate of progression-free survival at 4 years was 83% (95% CI, 73 to 88) in the rituximab group versus 64% (95% CI, 55 to 73) in the observation group (P<0.001). The rate of overall survival was 89% (95% CI, 81 to 94) in the rituximab group versus 80% (95% CI, 72 to 88) in the observation group (P=0.04). According to a Cox regression unadjusted analysis, the rate of overall survival at 4 years was higher in the rituximab group than in the observation group (hazard ratio for death, 0.50; 95% CI, 0.26 to 0.99; P=0.04).

CONCLUSIONS

Rituximab maintenance therapy after transplantation prolonged event-free survival, progression-free survival, and overall survival among patients with mantle-cell lymphoma who were younger than 66 years of age at diagnosis. (Funded by Roche and Amgen; LyMa ClinicalTrials.gov number, NCT00921414.)

Mantle-cell lymphoma, which is characterized by a specific immunophenotype and the chromosomal translocation t(11;14),[1] accounts for approximately 6% of non-Hodgkin's lymphomas among adults. After treatment, most patients have a relapse, and the duration of response decreases with each successive salvage therapy.[2,3]

One of the commonly recommended first-line treatments for patients who are eligible (according to standard guidelines) to undergo transplantation includes combined treatment with rituximab and high-dose cytarabine followed by autologous stem-cell transplantation.[4,5] Recently, a phase 3 prospective trial showed an advantage of alternating a chemotherapy regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and a regimen consisting of rituximab, dexamethasone, high-dose cytarabine, and a platinum derivative (R-DHAP), as compared with the R-CHOP regimen alone, before transplantation.[6] Young patients with untreated mantle-cell lymphoma who received the R-CHOP and R-DHAP regimens had longer progression-free survival and a longer duration of remission than those who received the R-CHOP regimen alone, but they did not have longer overall survival.

The lack of a plateau on the survival curve in the results of the prospective trials that have been published to date[6-8] suggests that residual tumor cells may persist after the end of treatment and that these may drive relapses. Thus, we hypothesized that maintenance therapy may prolong the duration of complete response and reduce the risk of relapse.

Rituximab, a monoclonal antibody targeting CD20, has shown a good safety profile and high efficiency in patients with various B-cell lymphomas. Prospective trials have investigated maintenance therapy with rituximab.[9-11] The European Mantle Cell Lymphoma Network found that among elderly patients who had an initial response to R-CHOP, rituximab maintenance therapy until disease progression prolonged both progression-free survival and overall survival.[12] Rituximab maintenance therapy is currently not recommended after transplantation.

We conducted a randomized, prospective, phase 3 trial to investigate the role of rituximab maintenance therapy in patients with mantle-cell lymphoma who had undergone autologous stem-cell transplantation. Because cytarabine plays a major role before transplantation in patients with mantle-cell lymphoma, four courses of R-DHAP were used as induction therapy. R-DHAP is an immunochemotherapy regimen without alkylating and anthracycline agents. To reduce the risk of long-term toxic effects, we used a transplantation conditioning regimen without total-body irradiation. The primary end point of the trial was event-free survival as evaluated from the date of randomization.

Methods

Characteristics of the Patients

The trial included patients 18 to 65 years of age who had untreated mantle-cell lymphoma and were eligible to undergo autologous stem-cell transplantation, who had disease of Ann Arbor stage II through IV (on a four-stage scale on which stage I indicates localized disease and increasing stage indicates more widespread disease), and who had an Eastern Cooperative Oncology Group (ECOG) performance-status score of less than 3 (on a 5-point scale, with higher numbers indicating increasing disability). Patients who were positive for the human immunodeficiency virus or those who presented with major coexisting conditions at diagnosis that were not related to lymphoma were excluded. The eligibility criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org. The diagnosis of mantle-cell lymphoma was established by local expert pathologists and reviewed centrally by pathology experts according to the 2008 World Health Organization classification. All the patients provided written informed consent.

Trial Protocol

Patients were included in the trial at the time of diagnosis. In brief, patients received induction chemotherapy with four courses of R-DHAP, repeated every 21 days. According to local practice (or in case of renal failure during treatment), investigators were allowed to use carboplatin or oxaliplatin instead of cisplatin. Stem cells were obtained according to local practice, after the third or fourth course of R-DHAP. The use of a chemotherapy regimen for stem-cell mobilization was not authorized.

Tumor status was assessed according to the

1999 International Working Group criteria by local investigators (see the Supplementary Appendix). After four courses of R-DHAP, patients who were having a partial response and whose tumor mass had been reduced by less than 75%, as assessed by means of computed tomography (CT), received a rescue induction therapy with four courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), administered as one course every 14 days. Only patients who were having a response, including those in complete remission (confirmed or unconfirmed) and those having a partial response (whose tumor mass was reduced by ≥75% after induction), were eligible to undergo transplantation. A minimal peripheral-blood progenitor-cell graft of 2×10^6 CD34+ cells per kilogram of body weight was required.

The conditioning regimen before transplantation was R-BEAM (rituximab, carmustine, etoposide, cytarabine, and melphalan). After transplantation and up to 3 months later, patients were randomly assigned to receive rituximab maintenance therapy or to undergo observation. The schedule for maintenance therapy was the receipt of 375 mg of rituximab per square meter of body-surface area, administered intravenously every 2 months for 3 years. The total number of planned doses of rituximab was 23 (4 doses administered with induction therapy, 1 dose with the preparative regimen for transplantation, and 18 doses over the 3 years of maintenance therapy). The trial protocol is available at NEJM.org.

OVERSIGHT

This unblinded, randomized prospective trial was performed according to the principles of the Declaration of Helsinki, and the protocol was approved by an ethics committee. The trial began before it was registered on ClinicalTrials.gov owing to an administrative error. A total of 29 patients were enrolled before registration. The first author and the last two authors designed the trial. Data were gathered by the investigators and by the sponsor and were analyzed by LYSARC (the academic research organization of the Lymphoma Study Association [LYSA]). All the authors had access to the data. The first author wrote the initial draft of the manuscript. All the authors contributed to the subsequent drafts, reviewed them, and jointly decided to submit the manuscript for publication. All the authors vouch for the integrity, accuracy, and completeness of the data and analyses and for the fidelity of the trial to the protocol. Roche supplied rituximab for the R-BEAM regimen and for maintenance therapy and funded the trial but did not contribute to the protocol design, trial execution, data collection or analysis, the writing of the manuscript, or the decision to submit the manuscript for publication.

STAGING, MONITORING, AND END POINTS

At the time of inclusion, the disease characteristics of the patients were assessed by means of clinical examination, standard biologic variables, bone marrow biopsy, and CT scan (neck, chest, abdomen, and pelvis). Response to therapy was assessed after the receipt of four courses of R-DHAP (and after R-CHOP in patients who received salvage therapy) and after transplantation. Randomization was stratified, in a 1:1 ratio, according to the use or nonuse of R-CHOP before transplantation.

The primary end point was event-free survival after randomization. Events were defined as disease progression, relapse, death, severe infection (grade 4 with life-threatening severity), or allergy to rituximab that led to the discontinuation of treatment after randomization. Secondary end points were progression-free survival (i.e., freedom from disease progression, relapse, and death from any cause) and overall survival as assessed from inclusion and from randomization. The trial design and follow-up assessments are described in detail in the Supplementary Appendix.

STATISTICAL ANALYSIS

Event-free survival was monitored and analyzed according to a group-sequential plan that included one interim analysis in order to allow for early stopping on the basis of efficacy. The total sample of 299 patients provided the trial with 80% power to detect a difference of 13 percentage points in the rate of event-free survival at 4 years (expected rates of 83% in the rituximab group vs. 70% in the observation group) at an alpha level of 0.05. O'Brien–Fleming boundaries were used to check for type I error, with the overall alpha level being 0.05 for the number of patients who were included at the time of data cutoff. The interim analysis was performed when at least 82 patients had reached 3 years after transplantation. The significance level for the

interim analysis was set at 0.0051, and the significance level for the final analysis was set at 0.0475. At the interim analysis, with a median follow-up of 34 months after transplantation, the rate of event-free survival ($P=0.006$ by the log-rank test) was under the O'Brien–Fleming boundary. The present analysis is the final analysis.

The intention-to-treat population included all the patients who had undergone randomization, and the primary and secondary end points were evaluated with the inclusion of all patients who had protocol violations or withdrew. The included-patients population constituted all the patients who provided written informed consent.

Time-to-event survival curves were estimated with the use of the Kaplan–Meier method. Time-to-event end points in the different groups were compared with the use of log-rank tests and Cox proportional-hazards regression. Patients who withdrew (e.g., all the patients who did not undergo randomization for any reason) and patients who were lost to follow-up (e.g., all the patients who underwent randomization and for whom an outcome was not updated for >1 year at the time of the final analysis) who did not have an event, as defined in the protocol at the time of the final analysis, had their data censored at the time of their last visit. Response rates were expressed in percentages with 95% exact confidence intervals that were based on the Clopper–Pearson method. All the statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

TREATMENT

From September 2008 through August 2012, we enrolled 299 patients in the study (Fig. 1). The characteristics of the patients at the time of inclusion are shown in Table 1. The central pathological review confirmed the diagnosis in all patients (by means of immunochemical testing for immunophenotype, except in 5 patients in whom the diagnosis was made by means of fluorescence in situ hybridization of blood samples) except for 1, whose disease was classified as hairy-cell leukemia (this patient was retained in the included-patients population but did not undergo randomization).

One course of cyclophosphamide, vincristine, and prednisolone was administered to 35 patients (12%) before the initiation of R-DHAP induction therapy. Carboplatin was used from the first course of R-DHAP in 76 patients, and oxaliplatin was used in 38; the remainder received cisplatin. The overall response rate after induction therapy was 94%, including a complete response in 124 patients (41%) and an unconfirmed complete response in 107 (36%). The main reasons to stop treatment during induction therapy were disease progression (in 5 patients) and toxic effects (in 7) (Fig. 1). All the patients who had renal toxic effects had received cisplatin. R-CHOP was administered in 20 patients who had an insufficient response after R-DHAP, and 10 of these patients proceeded to transplantation (3 patients were having a complete remission, 6 were having an unconfirmed complete remission, and 1 was having a partial response).

Overall, 257 of 299 patients (86%) underwent transplantation. After transplantation, 168 of 257 patients (65%) had a complete remission, and 61 (24%) had an unconfirmed complete remission. A total of 240 of 299 patients (80%) underwent randomization and constituted the intention-to-treat population; 120 patients were randomly assigned to the group that received rituximab maintenance therapy and 120 to the observation group. There was no significant difference between the two groups regarding the characteristics at enrollment (inclusion) and the patients' disease status at randomization (Table 1).

OUTCOME

At the stopping date (July 1, 2015), the median follow-up from inclusion was 54.4 months (range, 52.7 to 59.2), and the median follow-up from randomization was 50.2 months (range, 46.4 to 54.2). In the included-patients population, the median progression-free survival and median overall survival, as calculated from inclusion, were not reached. Among these patients, the 4-year rate of progression-free survival was 68% (95% confidence interval [CI], 62 to 73), and the 4-year rate of overall survival was 78% (95% CI, 73 to 82). According to the Mantle Cell Lymphoma International Prognostic Index (MIPI),[14] which is used to assess risk on the basis of age, ECOG performance-status score, lactate dehydrogenase level, and white-cell count (see the Supplementary Appendix), the median progression-free survival and overall survival were not reached among low-risk and intermediate-risk patients;

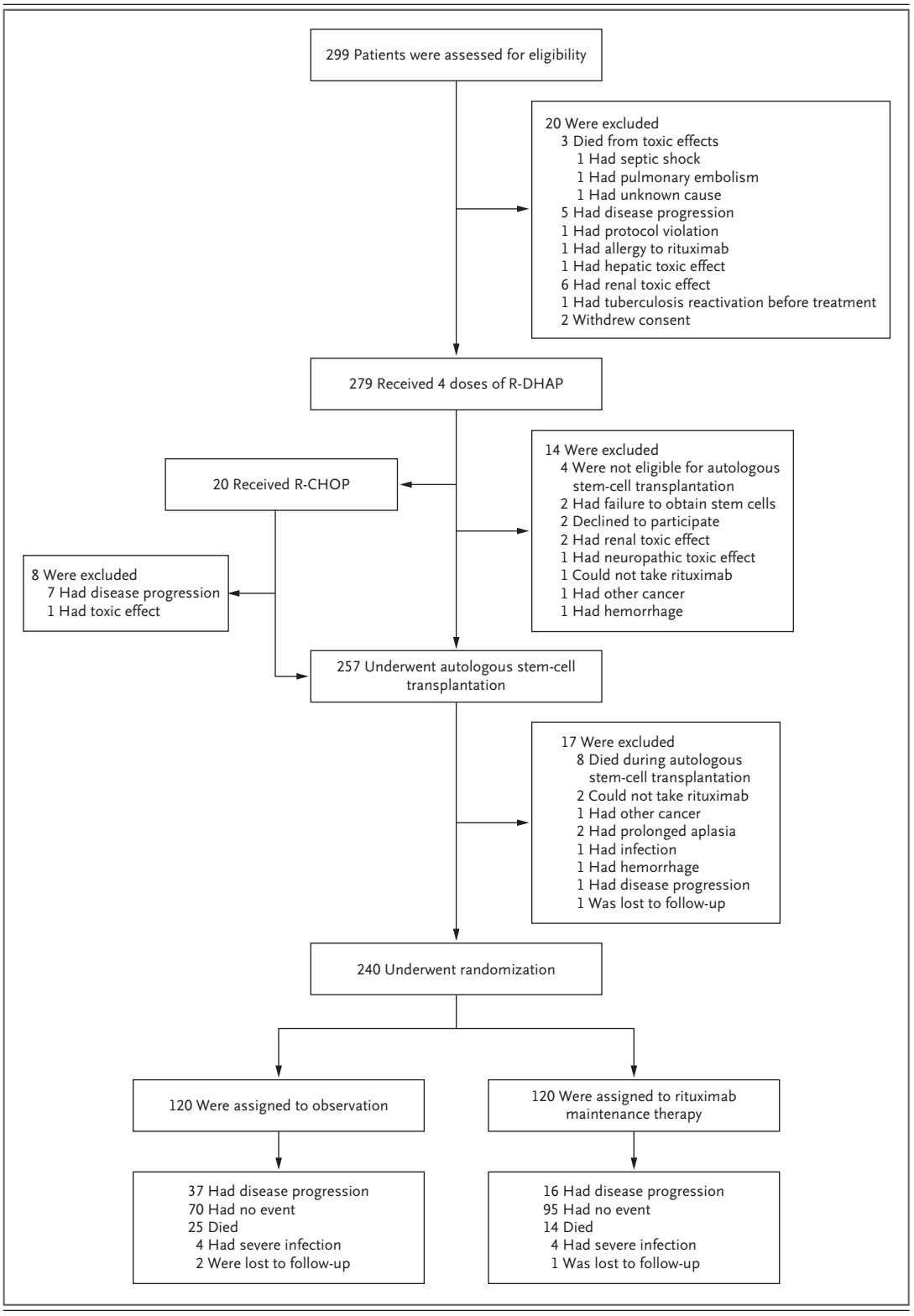

Figure 1 (facing page). Eligibility Assessment, Treatment, Randomization, and Follow-up of the Patients.

The R-DHAP regimen consisted of rituximab, dexamethasone, high-dose cytarabine, and a platinum derivative. A total of 20 patients who received all four courses of the R-DHAP regimen then received the R-CHOP regimen, which consisted of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. After autologous stem-cell transplantation, 120 patients were assigned to receive rituximab maintenance therapy and 120 were assigned to the observation group.

among high-risk patients, the median progression-free survival was 47.4 months and the median overall survival was 56.2 months (P<0.001 for both comparisons with the low-risk group). (Results regarding progression-free survival and overall survival that were calculated from inclusion and according to MIPI score are provided in Figs. S2 through S5 in the Supplementary Appendix.)

According to the protocol definition, 25 patients (21%) had an event in the rituximab group, as compared with 47 (39%) in the observation group. A total of 83 patients in the rituximab group completed the scheduled 3-year course of therapy. The main reasons to stop maintenance therapy were disease progression (in 16 patients) and neutropenia (in 9). Serious infection after transplantation was observed in 4 patients in each group (spondylitis, pyelonephritis, septicemia, and varicella pneumonia in 1 patient each in the rituximab group and septicemia, cellulitis, meningitis, and severe pneumonia in both lungs in 1 patient each in the observation group).

Information regarding grade 3 and 4 toxic effects, according to randomization and trial period, is provided in Table S1 in the Supplementary Appendix. In brief, the most frequent toxic event of grade 3 or 4 was neutropenia. A second cancer caused death in 3 patients in the rituximab group and in 1 in the observation group. No late effect of rituximab has been reported so far in either trial group. After randomization, 16 patients had disease progression and 13 patients died in the rituximab group, as compared with 37 patients who had disease progression and 24 who died in the observation group. The major cause of death in each group was lymphoma (in 8 patients in the rituximab group and 16 in the observation group).

The median event-free survival from randomization was not reached in either group (Fig. 2A). The 4-year rate of event-free survival as calculated from randomization was 79% (95% CI, 70 to 86) in the rituximab group, as compared with 61% (95% CI, 51 to 70) in the observation group (P=0.001), with a hazard ratio for disease progression, relapse, death, rituximab allergy, or severe infection of 0.46 (95% CI, 0.28 to 0.74; P=0.002).

The median progression-free survival and overall survival from randomization were not reached in either group. The 4-year rates of progression-free survival and overall survival were significantly higher in the rituximab group than in the observation group. The rate of progression-free survival was 83% (95% CI, 73 to 88) in the rituximab group, as compared with 64% (95% CI, 55 to 73) in the observation group (hazard ratio for disease progression, relapse, or death, 0.40; 95% CI, 0.23 to 0.68; P<0.001) (Fig. 2B). The rate of overall survival was 89% (95% CI, 81 to 94) in the rituximab group, as compared with 80% (95% CI, 72 to 88) in the observation group (hazard ratio for death, 0.50; 95% CI, 0.26 to 0.99; P=0.04) (Fig. 2C). The per-protocol analysis yielded similar results (see the Supplementary Appendix).

A total of 11 patients received R-CHOP before randomization; of these patients, 4 were assigned to the rituximab group (1 patient had disease progression and died and 3 did not have a relapse and were alive at the time of the final analysis) and 7 to the observation group (4 patients had a relapse and were alive at the time of the final analysis and 3 died). Among the 59 patients who did not undergo randomization, the median progression-free survival was 11.0 months (95% CI, 6.4 to 28.0), and the median overall survival was 30.6 months (95% CI, 12.3 to 44.6).

DISCUSSION

Rituximab maintenance therapy that was administered every other month for 3 years after transplantation prolonged event-free survival, progression-free survival, and overall survival

Table 1. Demographic and Clinical Characteristics of the Patients at the Time of Inclusion in the Trial.*

Characteristic	Patients Who Underwent Randomization (N=240)	Observation Group (N=120)	Rituximab Maintenance Group (N=120)	Patients Who Did Not Undergo Randomization (N=59)†	All Patients in the Included Population (N=299)
Age — yr					
Median	57	56	58	58	57
Range	27–65	29–65	27–65	41–65	27–65
Male sex — no. (%)	189 (79)	97 (81)	92 (77)	47 (80)	236 (79)
Ann Arbor stage — no./total no. (%)					
II	12/239 (5)	5/120 (4)	7/119 (6)	6/59 (10)	18/298 (6)
III	31/239 (13)	16/120 (13)	15/119 (13)	0/59	31/298 (10)
IV	196/239 (82)	99/120 (82)	97/119 (82)	53/59 (90)	249/298 (84)
B symptoms — no. (%)‡	64 (27)	27 (22)	37 (31)	25 (42)	89 (30)
ECOG performance-status score <3 — no. (%)§	230 (96)	113 (94)	117 (98)	52 (88)	282 (94)
Bone marrow involvement — no. (%)	149 (62)	73 (61)	76 (63)	43 (73)	192 (64)
Lactate dehydrogenase >ULN — no./total no. (%)	79/236 (33)	46/118 (39)	33/118 (28)	29/56 (52)	108/292 (37)
MIPI score — no. (%)¶					
Low risk	133 (55)	63 (52)	70 (58)	26 (44)	159 (53)
Intermediate risk	65 (27)	31 (26)	34 (28)	17 (29)	82 (27)
High risk	42 (18)	26 (22)	16 (13)	16 (27)	58 (19)
Percent of Ki-67–positive cells >30% — no./total no. (%)	61/175 (35)	29/83 (35)	32/92 (35)	15/41 (37)	76/216 (35)
Variant mantle-cell lymphoma — no./total no. (%)‖					
On local review					
Blastoid	24/239 (10)	12/119 (10)	12/120 (10)	11/59 (18.6)	35/298 (12)
Pleomorphic	6/239 (3)	5/119 (4)	1/120 (1)	1/59 (2)	7/298 (2)
On central review					
Blastoid	7/175 (4)	5/80 (6)	2/95 (2)	5/35 (14)	12/210 (6)
Pleomorphic	21/175 (12)	11/80 (14)	10/95 (11)	6/35 (17)	27/210 (13)

R-CHOP before autologous stem-cell transplantation — no. (%)	11 (5)	7 (6)	4 (3)	9 (15)	20 (7)
Disease status — no. (%)**					
After receipt of 4 courses of R-DHAP					
Overall response	236 (98)	117 (98)	119 (99)	31 (53)	267 (89)
Complete remission or unconfirmed complete remission	206 (86)	104 (87)	102 (85)	25 (42)	231 (77)
After autologous stem-cell transplantation					
Overall response	240 (100)	120 (100)	120 (100)	8 (14)	248 (83)
Complete remission or unconfirmed complete remission	223 (93)	110 (92)	113 (94)	7 (12)	230 (77)
Time from autologous stem-cell transplantation to randomization — mo					
Median	2.1	2.1	2.1	—	2.1
Range	0.4–4.2	0.4–3.9	0.4–4.2	—	0.4–4.2

* There was no significant difference between the two randomized groups regarding the characteristics at the time of inclusion and disease status before randomization. The intention-to-treat population included all the patients who had undergone randomization, and the included-patients population constituted all the patients who had provided written informed consent. R-CHOP denotes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP rituximab, dexamethasone, high-dose cytarabine, and a platinum derivative; and ULN upper limit of the normal range.

† The reasons that 59 patients included in the trial did not undergo randomization were disease progression (13 patients), death from toxic effects during induction therapy or autologous stem-cell transplantation (11), renal toxic effects (8), toxic effects in other organs (3), allergy to rituximab or inability to take rituximab (4), withdrawal of consent or decision by the patient to not undergo randomization (4), ineligibility for autologous stem-cell transplantation (4), failure to obtain stem cells (2), infection (2), prolonged neutropenia after autologous stem-cell transplantation (2), hemorrhage (2), other cancer (2), protocol violation (1), and unknown reason (1).

‡ B symptoms are systemic symptoms such as weight loss, night sweats, and fever.

§ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher numbers indicating increasing disability. A score of less than 3 indicates that the patient is at least ambulatory and capable of all self-care, although he or she may be unable to carry out any work activities, and that the patient is out of bed more than 50% of waking hours.

¶ The Mantle Cell Lymphoma International Prognostic Index (MIPI) is used in patients with mantle-cell lymphoma to assess risk on the basis of age, ECOG performance-status score, lactate dehydrogenase level, and white-cell count (see the Supplementary Appendix).

‖ Patients who did not present with a blastoid or pleomorphic cytologic variant of follicular lymphoma had a classic variant.

** Disease status was assessed according to the criteria of Cheson et al.[13]

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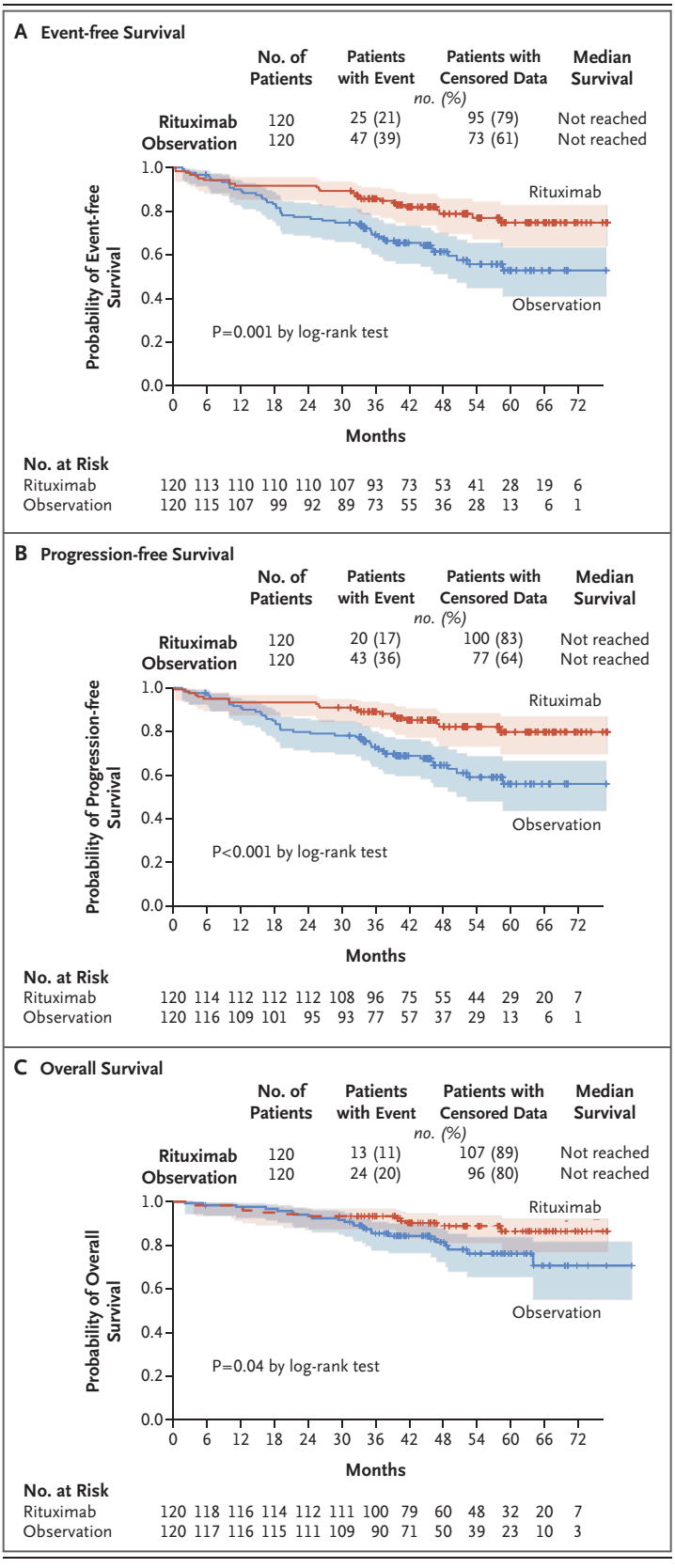

Figure 2. Event-free Survival, Progression-free Survival, and Overall Survival.

The Kaplan–Meier analyses of event-free survival, progression-free survival, and overall survival were performed according to trial group. Survival was calculated from the time of randomization. Event-free survival was defined as freedom from disease progression, relapse, death, allergy to rituximab, and severe infection. The hazard ratio for progression, relapse, death, rituximab allergy, or infection was 0.46 (95% CI, 0.28 to 0.74; P=0.002) (Panel A). Tick marks indicate censored data, and the shaded areas 95% confidence intervals. Progression-free survival was defined as freedom from disease progression, relapse, and death from any cause. The hazard ratio for progression, relapse, or death was 0.40 (95% CI, 0.23 to 0.68; P<0.001) (Panel B). In the analysis of overall survival, the hazard ratio for death was 0.50 (95% CI, 0.26 to 0.99; P=0.04) (Panel C).

among patients with mantle-cell lymphoma who were younger than 66 years of age. These results show the efficacy of a cytarabine-based induction regimen free of anthracycline or alkylating agents in patients with this condition.

Among patients with chemotherapy-sensitive disease who had a response to induction therapy and transplantation and received rituximab maintenance therapy, the 4-year rate of progression-free survival was 83%, and the 4-year rate of overall survival was 89%. Maintenance therapy with rituximab after R-DHAP induction therapy, followed by R-BEAM consolidation therapy, prevented relapses and was associated with a low risk of major infection. Whether maintenance therapy with rituximab improves outcomes in patients who are treated with other regimens is unknown.

The prolongation in overall survival that was observed in this trial suggests that the delivery of maintenance therapy beyond 3 years might be questionable. We did not measure changes in immunoglobulin levels and are unable to assess the degree and duration of immune suppression that are associated with this approach to treatment. We did not detect a higher rate of infectious complications in the rituximab group than in the observation group. Because status regarding minimal residual disease can predict outcome in patients, it could be postulated that patients with negative minimal residual disease status (i.e., those with a level of disease below the threshold of detection) after transplantation may not benefit from maintenance therapy. However,

this question has not been addressed. In addition to monitoring for minimal residual disease, ^{18}F-fluorodeoxyglucose–positron-emission tomography (FDG-PET) could also be a useful tool to drive medical decision making regarding the use of maintenance therapy after transplantation. Monitoring for minimal residual disease and FDG-PET were performed in the present trial but were not used for decision making.

The use of high-dose cytarabine plus rituximab is recommended in young patients with mantle-cell lymphoma. The most common regimens — that is, alternating R-CHOP or R-DHAP, the alternative maxi-CHOP regimen with high-dose cytarabine (Nordic MCL2 protocol), and R-hyper-CVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone)[6,7,15] — combine rituximab and cytarabine, alkylating agents, and an anthracycline. We reasoned, on the basis of results from previous clinical trials, that cytarabine and platinum derivatives alone might be sufficient to induce a response rate similar to that seen in combined protocols that have used regimens with anthracyclines or alkylating agents. The rates of response and complete response after the administration of R-DHAP in the trial population seem to be similar to those that have been observed with regimens including anthracycline or alkylating agents. R-DHAP induction therapy has several advantages, including its easy use in daily practice, short duration, and low doses of cytarabine. In addition, it has no late cardiac toxic effects. Among the 184 patients who received cisplatin in the first course of chemotherapy, 27 switched to carboplatin and 38 switched to oxaliplatin. In contrast, only 1 patient who was treated with carboplatin switched to cisplatin, and 1 who was treated with oxaliplatin switched to carboplatin. In view of the toxicity of cisplatin, a prospective trial addressing the choice of platinum compound in chemotherapy for lymphoma is warranted.

The most commonly used conditioning regimens are BEAM (carmustine, etoposide, cytarabine, and melphalan), BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide), and a total-body irradiation–based regimen.[6,7] The role of total-body irradiation is still a matter of debate because it is not available in all centers and is associated with considerable short-term and long-term toxic effects. Our results with regard to progression-free survival and overall survival are in line with those of the Nordic Lymphoma Group and suggest that total-body irradiation–based conditioning regimens may not be superior to chemotherapy alone when an effective regimen is used during induction.[8,15,16]

In conclusion, our trial showed that an induction regimen with four courses of R-DHAP followed by transplantation without total-body irradiation resulted in a high rate of complete response. A 3-year course of rituximab maintenance therapy administered every 2 months prolonged overall survival among young patients with mantle-cell lymphoma.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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