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High Rate of Durable Remissions After Treatment of Newly Diagnosed Aggressive Mantle-Cell Lymphoma With Rituximab Plus Hyper-CVAD Alternating With Rituximab Plus High-Dose Methotrexate and Cytarabine

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To determine the response, failure-free survival (FFS), and overall survival rates and toxicity of rituximab plus an intense chemotherapy regimen in patients with previously untreated aggressive mantle-cell lymphoma (MCL).

Patients and Methods
This was a prospective phase II trial of rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD; considered one cycle) alternating every 21 days with rituximab plus high-dose methotrexate-cytarabine (considered one cycle) for a total of six to eight cycles.

Results
Of 97 assessable patients, 97% responded, and 87% achieved a complete response (CR) or unconfirmed CR. With a median follow-up time of 40 months, the 3-year FFS and overall survival rates were 64% and 82%, respectively, without a plateau in the curves. For the subgroup of patients ≤ 65 years of age, the 3-year FFS rate was 73%. The principal toxicity was hematologic. Five patients died from acute toxicity. Four patients developed treatment-related myelodysplasia/acute myelogenous leukemia, and three patients died while in remission from MCL. A total of eight treatment-related deaths (8%) occurred.

Conclusion
Rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine is effective in untreated aggressive MCL. Toxicity is significant but expected. Because of the shorter FFS concurrent with significant toxicity in patients more than 65 years of age, this regimen is not recommended as standard therapy for this age subgroup. Larger prospective randomized studies are needed to define the role of this regimen in the treatment of MCL patients compared with existing and new treatment modalities.

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INTRODUCTION

Mantle-cell lymphoma (MCL) is a well-recognized entity with discrete clinicopathologic features as defined in the WHO classification.[1] Three histopathologic patterns have been described, including a mantle-zone variant that, in our experience, behaves similar to indolent lymphomas.[2] The two other patterns (diffuse and nodular) are much more aggressive and respond poorly to conventional doxorubicin-containing chemotherapy, with complete remission rates of 20% to 50%, median failure-free survival (FFS) times of 10 to

18 months, and median overall survival (OS) times of 2 to 4 years.[3-8] In addition, a blastoid variant of MCL has been described that is associated with a poor prognosis.[9]

The monoclonal anti-CD20 antibody rituximab has shown activity in untreated patients with MCL.[10] Addition of this agent to the combination regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has resulted in an overall response rate of 98% and a complete response (CR)/unconfirmed CR (CRu) rate of 48% but a median FFS time of only 16 months.[11]

Fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with high doses of methotrexate and cytarabine has proven to be an effective cytoreductive regimen in patients with aggressive histopathologic variants of MCL. One study reported an overall response rate of 93.5% (CR rate of 38%) after four cycles (one hyper-CVAD cycle, one high-dose methotrexate and cytarabine cycle, one hyper-CVAD cycle, and one high-dose methotrexate and cytarabine cycle) in a clinical trial designed to test only four cycles followed by high-dose chemotherapy and stem-cell transplantation.[12] In the present trial, we prospectively evaluated the effectiveness of six to eight cycles of the combination of this aggressive regimen with rituximab for the treatment of newly diagnosed aggressive MCL.

PATIENTS AND METHODS

Patient Eligibility

Patients with newly diagnosed aggressive variants of MCL were enrolled onto a prospective clinical trial approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center after signing an approved informed consent form. These patients had either the diffuse or the nodular patterns of MCL and also could present with the blastoid variant. Patients with MCL with a pure mantle-zone pattern were excluded. Other eligibility criteria included age greater than 16 years (no upper limit), good performance status (Zubrod score of 2 or less),[13] and adequate organ function as determined by a cardiac ejection fraction of $\geq$ 50%, a serum bilirubin level of less than 1.5 mg/dL, and a serum creatinine level of less than 2 mg/dL. In addition, the study required an absolute neutrophil count of $\geq$ 1,000/μL and platelet counts of $\geq$ 100,000/μL unless a lower value was caused by lymphoma. In addition, all patients had to agree to receive transfusion of blood products as needed. Patients were ineligible if they had CNS involvement, were HIV positive, were pregnant, had comorbid physical or mental illnesses that precluded treatment, or had a second malignancy that resulted in less than a 90% predicted chance of 5-year survival.

Pretreatment Clinical Evaluation

Pretreatment evaluation included a physical examination; a chest radiograph; computed tomography (CT) scans of the chest, abdomen, and pelvis; bilateral bone marrow biopsies and aspiration; and a gallium or a positron emission tomography (PET) scan. In addition, blood was drawn for serum chemistry analysis, a CBC count with differential analysis, measurement of serum beta$_2$-microglobulin level, and flow cytometric analysis of lymphocyte membrane surface markers. Because of a suspected high prevalence of GI involvement, the protocol required pretreatment esophagogastroduodenoscopy and colonoscopy in each patient, with biopsies of gross abnormal areas or random biopsies if no abnormal areas were identified.

Pathologic Analysis

All pathologic materials were reviewed for confirmation of the diagnosis and classification using the WHO classification.[1] The neoplasm in each lymph node biopsy specimen was further subclassified as having a nodular or diffuse pattern, as described previously.[2]

All initial diagnostic biopsy specimens were assessed for cyclin D1 expression using fixed, paraffin-embedded tissue section. Other B-cell and T-cell markers, most commonly CD5 and CD20, were also tested for. Bone marrow and peripheral-blood specimens were analyzed using flow cytometry. A classical polymerase chain reaction technique was used to detect the presence of t(11;14)(q13;q32) involving the major translocation cluster for the *bcl-1* locus, as previously described.[14] In addition, fluorescence in situ hybridization analysis was used to assess for the presence of both the 11q13 and (11;14) break points.[15] The diagnosis of MCL in every patient in this study was based on compatible morphologic and immunophenotypic findings with expression of cyclin D1 and/or detection of t(11;14)(q13;q32). Endoscopic biopsies of each site of the GI tract were labeled and assessed separately. In each patient in this study in whom GI tract involvement of MCL was considered to be present, at least one (usually two and rarely three) biopsy specimen was assessed immunohistochemically for the presence of CD5, CD20, and cyclin D1 using fixed, paraffin-embedded tissue sections. In 14 patients, a lymph node was not available to biopsy. The diagnosis in these patients was made by examination of GI, bone marrow, and/or peripheral-blood specimens.

Chemotherapy

The treatment schema is depicted in Table 1. Cycle 1 was a 21-day cycle administered either on an outpatient or inpatient

Table 1. Doses and Schedule

Cycles 1, 3, 5, 7: Rituximab Plus Hyper-CVAD	Cycles 2, 4, 6, 8: Rituximab Plus Methotrexate/Cytarabine
Rituximab 375 mg/m^2 D 1	Rituximab 375 mg/m^2 D 1
Cyclophosphamide 300 mg/m^2 IV over 3 hrs q $\times$ 12 hrs 6 D 2-4	Methotrexate 200 mg/m^2 IV over 2 hrs D 2
Doxorubicin 16.6 mg/m^2/d IVCI 72 hrs D 5-7	Methotrexate 800 mg/m^2 IVCI 22 hrs D 2
Vincristine 1.4 mg/m^2 IV (maximum 2 mg) D 5 & D 12	Cytarabine 3,000* mg/m^2 IV over 2 hrs q 12 hrs $\times$ 4 D 3-4
Dexamethasone 40 mg IV or PO D 2-5 and D 12-15	

NOTE. Alternate cycles 1 and 2 every 21 days. Staging every two cycles—if CR/CRu after two cycles, give six total; if < CR/CRu after first six cycles, off study.

Abbreviations: hyperCVAD, fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; CR, complete remission; CRu, complete remission unconfirmed; G-CSF, granulocyte colony stimulating factor; mg, milligrams; D, day; IVCI, intravenous continuous infusion; IV, intravenous; hrs, hours; q, every.

*Cytarabine dose reduced to only 1,000 mg/m^2/dose $\times$ 4 for age > 60 yr or creatinine > 1.5 mg/dL. Prophylaxis: mesna, G-CSF, antifungal, antibacterial, antiviral, calcium leucovorin (see text), prednisone eyedrops.

basis and consisted of rituximab 375 mg/m^2 on day 1, followed by cyclophosphamide 300 mg/m^2 per dose administered intravenously (IV) over 3 hours every 12 hours for six doses on days 2, 3, and 4. One hour before the start of cyclophosphamide, mesna was started at 600 mg/m^2 per dose IV over 24 hours daily on days 2, 3, and 4 and completed 12 hours after the administration of the last dose of cyclophosphamide. Doxorubicin was started 12 hours after the last dose of cyclophosphamide at 16.7 mg/m^2 IV continuous infusion over 24 hours daily on days 5, 6, and 7. Vincristine 1.4 mg/m^2 (maximum absolute dose = 2 mg) was also administered IV piggyback 12 hours after the last dose of cyclophosphamide and was repeated on day 12 of the cycle. Dexamethasone 40 mg absolute dose was administered orally or IV on days 2 to 5 and 12 to 15 of the cycle. Patients with evidence of peripheral-blood involvement, as determined by flow cytometric analysis, at the time of initial presentation had their first dose of rituximab delayed or omitted at the discretion of the clinician if there was concern for risk of tumor lysis syndrome or cytokine-release syndrome.

Prophylaxis for course 1 included granulocyte colony-stimulating factor 5 μg/kg subcutaneously, valacyclovir 500 mg orally, fluconazole 100 mg orally, and levofloxacin 500 mg orally, all administered daily for 10 days starting 24 to 36 hours after the end of the infusion of doxorubicin. Later in the trial, ciprofloxacin was substituted for levofloxacin.

Cycle 2 was a 21-day cycle administered inpatient and consisted of rituximab 375 mg/m^2 on day 1, followed on day 2 by methotrexate 200 mg/m^2 administered IV over 2 hours, followed by methotrexate 800 mg/m^2 IV over 22 hours. Before the start of methotrexate, the urine was alkalinized to a pH of 6.8 or more and kept at this level or higher until the methotrexate was cleared from the blood. For patients with initial serum creatinine levels greater than 1.5 mg/dL, the dose of methotrexate was decreased by 50%. In patients with evidence of third spacing of fluids, the fluid was tapped completely, or in the patients in whom this was not possible, rituximab plus hyper-CVAD was repeated for the next cycle until the third spacing of the fluid resolved (this situation was rare). Cytarabine was administered at a dose of 3 g/m^2 per dose over 2 hours every 12 hours for four doses on days 3 and 4 of the cycle. The dose of cytarabine was automatically reduced to only 1 g/m^2 per dose in patients older than 60 years and in patients with a serum creatinine level greater than 1.5 mg/dL. Prednisolone 1% ophthalmic solution, two drops in each eye four times daily, was started on the day of the start of cytarabine infusion and was continued for 7 days to prevent chemical conjunctivitis. Folinic acid (citrovorum factor) rescue therapy (50 mg) was administered orally 12 hours after the infusion of methotrexate was completed, followed by 15 mg orally initiated every 6 hours for eight doses. Serum methotrexate levels were checked at 24 and 48 hours after the end of the infusion, and doses of folinic acid were increased to 100 mg IV every 3 hours if the serum levels were either more than 1 μmol/L or more than 0.1 μmol/L at 24 or 48 hours, respectively.

Prophylaxis with cycle 2 was otherwise similar to that of cycle 1. The use of erythropoietin was permitted throughout therapy.

Evaluation During and After Treatment

The following tests were performed every two cycles: CT scans of the chest, abdomen, and pelvis; gallium or PET scan; bilateral bone marrow biopsies with unilateral aspiration; and esophagogastroduodenoscopy/colonoscopy with biopsies, as described earlier. After therapy was completed, the same studies (except for gallium/PET scans) were performed every 3 months during the first year, every 4 months during the second year, every 6 months during the third and fourth years, and yearly thereafter.

Number of Courses

Patients who achieved a CR after the first two cycles (one rituximab plus hyper-CVAD cycle and one rituximab plus methotrexate/cytarabine cycle) received four more cycles, for a total of six cycles. Patients who achieved a partial response (PR) after two cycles and a complete remission after six cycles received two more cycles, for a total of eight cycles. Patients with evidence of disease after six cycles were removed from the study.

Dose Adjustment As a Result of Toxicity

Grade 3 nonhematologic toxicity required a −1 dose level decrease of the offending drug. Grade 4 nonhematologic toxicity required a discussion with the principal investigator, followed by a determination regarding removal from the study.

Grade 3 to 4 hematologic toxicity during the nadir of each cycle did not require a dose adjustment. Instead, doses of myelotoxic drugs were adjusted according to the blood counts on day 21 of the cycle. The day-21 platelet count between 75 and 100,000/μL and/or absolute granulocyte count (AGC) between 750 and 1,000/μL warranted a delay until counts recovered to more than 100,000 platelets/μL and more than 1,000/μL AGC without a decrease in the dose; if the day-21 platelet count was less than 75,000/μL and/or the AGC was less than 750/μL, there was a delay in therapy until the platelet count increased to 100,000/μL and the AGC increased to 1,000/μL, and the next similar regimen was administered with one level of reduction in the dose of the myelotoxic drugs.

Response Criteria

Colonoscopy and upper endoscopy were required in addition to other established tests for response determination. Response criteria were according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma.[16] Treatment failure was defined as recurrence or progression of disease, death caused by disease or toxic effects, and death caused by treatment-related second malignancies.

Statistical Methods

Because of a historic precedent of adjusting treatment on the basis of patient age, our primary objective in this trial was to evaluate the efficacy of the combination regimen in patients aged 65 years or younger. The primary end point was the assessment of the FFS rate. Secondary end points were the rates of CR/CRu and OS and a determination of the toxicity of the regimen. Patients more than 65 years old were also eligible for the trial, and the protocol specified that the results for this group would be analyzed separately.

The original trial design specified enrollment of 35 patients aged ≤ 65 years and 15 patients aged more than 65 years. The total number of patients was later increased to 100 to gain better precision for the estimates of FFS in view of the early favorable results. Patient characteristics were tabulated into two groups on the basis of age. OS was measured from the start of treatment until the date of death or last follow-up. FFS was measured from the start of treatment until failure (as defined in Response Criteria) or until the last follow-up visit. Four patients who achieved a PR after six cycles and who were consolidated with stem-cell transplantation were not censored for the FFS analysis. Likewise, patients in remission from MCL who developed a treatment-related second malignancy were not censored for FFS analysis. The CR/CRu rate

achieved after the first six courses of therapy was calculated for the total group and for the two age subgroups. The Fisher's exact test was used to test for an association between CR and patient characteristics. The Kaplan-Meier product-limit method was used to estimate both FFS and OS.[17] The log-rank test[18] was used to test for differences in FFS and OS according to several variables including age, presence of bone marrow involvement, presence of GI involvement, presence of any amount of peripheral-blood involvement (as judged by morphologic assessment only), blastoid cytology, pretreatment serum levels of β_2-microglobulin and lactate dehydrogenase (LDH), presence of an enlarged spleen by CT criteria (as judged by the radiologist), and International Prognostic Index (IPI) score for aggressive non-Hodgkin's lymphoma.[19] $P < .05$ was deemed statistically significant. High β_2-microglobulin was defined as β_2-microglobulin $\geq$ 3 mg/L, and high LDH was defined as an LDH greater than the upper normal range (or 618 μ/L). All tests were two sided. The number of febrile neutropenic episodes and the frequency of dose adjustments were calculated by age and tested for a possible association using Fisher's exact method.

RESULTS

Clinical Characteristics

Between March 1999 and March 2002, 100 patients with untreated aggressive MCL were enrolled onto the study. One patient was deemed ineligible after having signed up but before the start of therapy because of a comorbid physical condition that precluded treatment (poor underlying pulmonary function not related to his lymphoma). Two patients refused treatment after having signed the consent form and never received therapy. Thus, 97 patients were treated in the study. Table 2 lists the pretreatment patient characteristics by age subgroup. Sixty-five patients were $\leq$ 65 years old, and 32 patients were more than 65 years old, for an overall median age of 61 years (range, 41 to 80 years). Most patients had normal LDH (76%) but elevated β_2-microglobulin (55%) in serum and presented with evidence of GI involvement (88%; mostly in the colon and, in 50% of patients, detected only after microscopic analysis). Ninety-six patients were classified as having Ann Arbor stage IV disease, of whom eight patients were upstaged after endoscopy with biopsy showed the disease to be present in the GI tract. All but two patients had a performance status of 0 to 1. The most common histopathologic pattern was diffuse, and 14% of these patients presented with the blastoid cytologic variant. Thirty-six patients (37%) had disease in the peripheral blood. Compared with patients who were 65 years of age or younger, patients who were more than 65 years of age more often tended to have high β_2-microglobulin and an IPI of more than 2.

In 14 patients, the histopathologic pattern could not be assessed because of lack of enlarged lymph nodes. These patients presented with disease in bone marrow, spleen, GI tract, and/or peripheral blood.

Table 2. Characteristics of 97 Patients

Characteristic	% of Patients		
	All Ages	≤ 65 Years	> 65 Years
No. of patients	97	65	32
Age, years			
Median	61		
Range	41-80		
Male-female ratio	3:1	3:1	3:1
Ann Arbor stage IV	99	98	100
Bone marrow involvement	91	89	94
GI involvement	88	85	94
Performance status, 0-1 Zubrod	98	98	97
Diffuse histologic pattern, n = 83*	89	88	88
Blastoid cytologic variant	14	14	16
Serum lactate dehydrogenase > normal	24	20	31
Serum/beta$_2$-microglobulin ≥ 3 mg/L	55	46	72
Peripheral blood involvement	49	35	41
Large spleen	40	40	41
International Prognostic Index > 2	57	34	91

*Fourteen patients had no lymph node to biopsy.

Response

Response was assessed every two cycles. Of the 97 patients, one died of unknown causes after an uneventful first cycle, another patient died from pulmonary hemorrhage during myelosuppression from cycle 2 before a restaging could be performed, and a third patient refused further therapy after only one cycle of chemotherapy. These patients are included in the response analysis and categorized as nonresponders. After the first six courses, a response was achieved in 97% of patients, of whom 87% achieved a CR/CRu (75 patients with CR and nine patients with CRu), and 10% achieved a PR. Thirty percent of the patients achieved CR/CRu after the first two cycles, 40% of patients achieved CR/CRu after four cycles, and 30% of patients achieved CR/CRu after six cycles. Table 3 lists the rates of CR overall and by patient characteristics. The CR rate was 89% and 84% in patients $\leq$ 65 years of age and patients older than 65 years of age, respectively. The CR rate was not significantly different among age groups ($P = .52$). The only variable associated with a lower CR/CRu rate was the presence of a pretreatment serum β_2-microglobulin level of $\geq$ 3 mg/L ($P = .01$).

FFS

Ninety-seven patients were assessable for analysis FFS and OS. Table 4 lists the estimated FFS and OS rates at 3 years for the entire population and by age group. The FFS and OS rates for the overall group were 64% and 82%, respectively, with no apparent plateau in the curves (Fig 1).

Of the 39 patients who experienced an event failure, 21 were $\leq$ 65 years old, for an estimated 3-year FFS rate in this subgroup of 73%, and 18 were more than 65 years old, for an estimated 3-year FFS rate in this subgroup of 50% (Fig

Table 3. CR/CRu Rates After Six Courses

Variable	CR/CRu Response Rate (%)	95% CI (%)	χ^2 P
Overall	87	79 to 93	
High serum beta$_2$-microglobulin			
No	98	88 to 100	
Yes	79	66 to 89	.01
High serum LDH			
No	91	81 to 96	
Yes	78	56 to 93	.15
GI			
Negative	91	59 to 100	
Positive	89	79 to 95	.16
IPI score			
≤ 2	93	81 to 99	
> 2	84	71 to 92	.10
Bone marrow involvement			
No	78	40 to 97	
Yes	89	80 to 94	.31
Blastoid cytology			
No	89	80 to 95	
Yes	79	49 to 95	.37
Age			
≤ 65 years	89	79 to 96	
> 65 years	84	67 to 95	.52
Enlarged spleen			
No	90	75 to 95	
Yes	85	69 to 94	.54
Age			
< 60 years	90	77 to 97	
61-65 years	88	64 to 99	
Peripheral blood			
No	89	75 to 95	
Yes	86	75 to 95	.76
IPI score			
≤ 1	89	52 to 100	
> 1	88	79 to 94	.99

Abbreviations: CR, complete response; CRu, complete response unconfirmed; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

2). The difference in FFS rates between these two age groups was statistically significant ($P = .02$). Other pretreatment variables associated with a shorter FFS rate included a serum β_2-microglobulin level of ≥ 3 mg/dL, a serum LDH level greater than normal, and an IPI score of greater than 2. Further analysis of pretreatment variables among age subgroups failed to show any association between a pretreatment variable and a shorter FFS for patients aged 65 years or younger. However, among patients older than 65 years, compared with the younger subgroup, a pretreatment serum β_2-microglobulin level of ≥ 3 mg/dL was associated with a shorter FFS at 3 years (38% *v* 78%, respectively; $P = .02$); the presence of peripheral-blood involvement was also associated with a shorter FFS at 3 years (31% *v* 63%, respectively; $P = .04$). A multivariate analysis could not be performed because of an insufficient number of events.

Table 4. Three-Year FFS and OS Estimates

Variable	No. of Patients	3-Year FFS (%)	P	3-Year OS (%)	P
Overall		65		82	
Serum beta$_2$-microglobulin ≥ 3 mg/L					
No	44	79	.001	87	.1
Yes	53	51		78	
Serum LDH normal					
No	74	74	.002	84	.87
Yes	23	39		77	
Age > 65 years					
No	65	75	.01	85	.05
Yes	32	50		75	
IPI > 2					
No	42	78	.03	87	.41
Yes	55	54		78	
GI involvement					
No	11	35	.1	89	.96
Yes	79	66		82	
Blastoid					
No	83	66	.33	86	.06
Yes	14	50		61	
Large spleen					
No	58	68	.36	81	.52
Yes	39	66		83	
Bone marrow involvement					
No	9	78	.25	83	.86
Yes	88	62		82	
Peripheral-blood involvement					
No	61	69	.22	86	.51
Yes	36	58		76	

Abbreviations: FFS, failure-free survival; OS, overall survival; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

Analysis of FFS According to Serum β_2-Microglobulin Levels and Age Group

Figure 3 shows FFS curves according to pretreatment serum β_2-microglobulin levels and age. FFS was similar among patients ≤ 65 years old regardless of the serum β_2-microglobulin level. However, a significant difference in FFS was found in patients more than 65 years of age according to pretreatment β_2-microglobulin levels, which is a finding that suggests an interaction between β_2-microglobulin and age in this age subgroup. However, no formal test of an interaction was possible because of the small number of observations.

OS

Of the 23 patients who died, 11 were ≤ 65 years old, for an estimated 3-year OS in this subgroup of 86%, and 12 were more than 65 years old, for an estimated 3-year OS in this subgroup of 74%. The difference between these two age subgroups was statistically significant ($P = .047$; Fig 4). Patients with blastoid cytology showed a tendency towards a shorter OS compared with patients without blastoid cytology. No other variable studied was significantly associated with a shorter OS time.

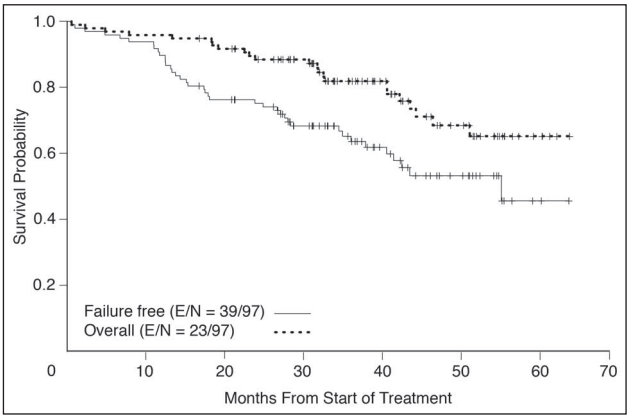

Fig 1. Failure-free and overall survival rates in 97 patients with newly diagnosed aggressive mantle-cell lymphoma treated with rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with rituximab plus methotrexate-cytarabine. With a median follow-up of 40 months, the 3-year failure-free and overall survival rates were 64% and 82%, respectively. E, events; N, total patients.

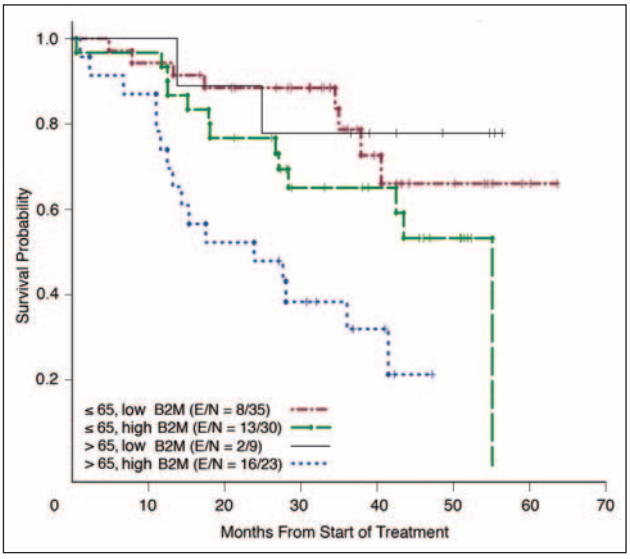

Fig 3. Failure-free survival by age subgroup according to pretreatment serum β_2-microglobulin (B2M) levels. The levels were of prognostic importance only for patients more than 65 years old ($P = .02$). E, events; N, total patients.

Toxicity

Twenty-nine percent of patients did not finish their intended number of cycles because of toxicity, and of these patients, 80% belonged to the group of patients scheduled to receive eight cycles of therapy. The distribution of patients who did not finish the intended number of cycles was similar by age group. The principal toxicity in the study was hematologic. The hematologic toxic effects are listed in Table 5. Rituximab plus hyper-CVAD and, to a greater extent, rituximab plus high-dose methotrexate-cytarabine produced significant grade 4 neutropenia and thrombocytopenia. There was a trend towards cumulative toxicity for thrombocytopenia after rituximab plus high-dose methotrexate-cytarabine.

Table 6 lists the nonhematologic toxic effects. Neutropenic fever occurred after 15% of the 602 courses administered. There were five toxic deaths during therapy, of which three were a result of neutropenic sepsis. One of these septic episodes was caused by *Staphylococcus aureus* infection, and two were caused by a levofloxacin-resistant Gram-negative organism (both patients < 60 years old and already in CR). After a change from levofloxacin to ciprofloxacin, no other cases of resistant Gram-negative sepsis occurred. A fourth patient died of pulmonary hemorrhage during the nadir of cycle two, presumably related to scarring from recently treated pulmonary aspergillosis. The fifth patient, who also was less than 60 years old, died of unknown causes before the start of the second cycle and after an uneventful first cycle.

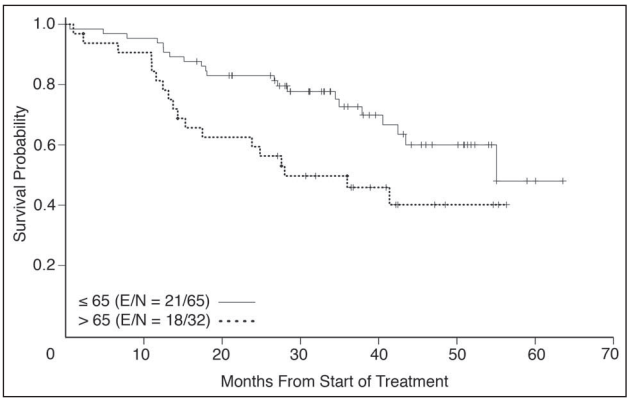

Fig 2. Failure-free survival (FFS) by age subgroup in 97 patients with newly diagnosed aggressive mantle-cell lymphoma treated with rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with rituximab plus methotrexate-cytarabine. With a median follow-up of 40 months, the 3-year FFS rate for patients more than 65 years old is 50% compared with 73% for patients 65 years or younger ($P = .02$). E, events; N, total patients.

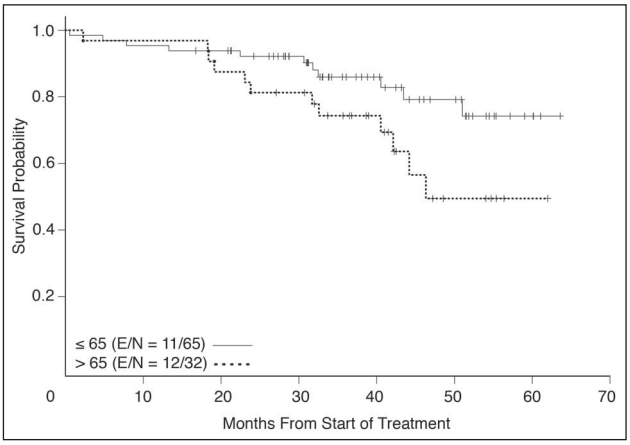

Fig 4. Overall survival (OS) according to age. With a median follow-up of 40 months, the 3-year OS rate for patients ≤ 65 years old was 86% compared with 74% for patients more than 65 years old ($P = .047$). E, events; N, total patients.

Table 5. Grade 4 Hematologic Toxic Effects After 602 Courses

Course No.	Neutropenia (%)		Thrombocytopenia (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
1	10	51	12.5	2
2	7	64	9	28
3	7	28	23	14
4	5	64	9	42
5	7	31	17	12
6	3	68	5	46
7	14	37	15	17
8	4	55	7	50

NOTE. Course Nos. 1, 3, 5, and 7 = rituximab plus fractionated cyclophosphamide; vincristine, doxorubicin, and dexamethasone; course Nos. 2, 4, 6, and 8 = rituximab plus methotrexate-cytarabine.

Three patients developed myelodysplasia (MDS) at 2.2 to 3 years after the start of treatment. All of the patients had diploid cytogenetics at the time of diagnosis and developed hypodiploid clones with −5, −7 (one patient), −7 (one patient), and del 7 (one patient). One of these patients was 54 years old and received a full treatment of eight alternating cycles (four cycles with fractionated cyclophosphamide); the second patient was 61 years old and received a total of six alternating cycles (three cycles with fractionated cyclophosphamide); the third patient was 79 years old and received five alternating cycles (three cycles with fractionated cyclophosphamide). All patients eventually died of MDS while in remission from MCL.

One patient developed acute myelogenous leukemia (AML) and is currently alive. Altogether, the overall mortality rate for the study was 8%.

Table 6. Nonhematologic Toxic Effects After 602 Cycles

Grade 3 to 4 Toxic Effect	No. of Events	%
Neutropenic fever*	80	13
R-HCVAD	20†	
R-Mtx/AraC	60†	
Infection*	35	6
Bacteremia	20	3
Pneumonia	6	1
Other	9	1.5
Fatigue	18	3
Stomatitis	6	1
Bleeding	3	0.5
Pancreatitis	1	0.1
Kidney failure	1	0.1
CNS	1	0.1

NOTE. Lethal acute toxicity occurred in five patients: sepsis (*Staphylococcus aureus, Escherichia coli, Proteus mirabilis*) = three patients; pulmonary hemorrhage = one patient; unknown cause = one patient.
Abbreviations: R-HCVAD, rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; R-Mtx/Ara-C, rituximab plus methotrexate and cytarabine.
*No difference for patients ≤ 65 years and patients > 65 years.
†$P = .00001$.

Analysis of Age, Dose, and Toxicity

Table 7 shows the relationship between age, chemotherapy regimen, and dose adjustment. Patients who had at least one level of drug adjustment at some point throughout treatment were assessed according to age and the chemotherapy regimen after which it occurred. The rate of dose adjustments (decrease in dose) caused by any toxic effect was significantly higher in the subgroup of patients more than 65 years of age compared with the subgroup of patients ≤ 65 years old ($P = .00001$). This was true despite the automatic pretreatment reduction in the dose of cytarabine to one third of the original dose for these patients. When analyzed according to regimen, rituximab plus high-dose methotrexate-cytarabine required more dose adjustments compared with rituximab plus hyper-CVAD ($P = .0002$).

Neutropenic febrile episodes occurred with similar frequency among patients more than 65 years old and patients ≤ 65 years old. However, neutropenic febrile episodes were more frequent after treatment with rituximab plus high-dose methotrexate-cytarabine ($P = .00001$).

DISCUSSION

Rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate-cytarabine is effective for patients with aggressive previously untreated MCL, achieving an overall CR/CRu rate of 87% and a 3-year FFS rate of 64% for the entire group after a median follow-up time of 40 months. The 3-year FFS rate increased to 73% in the subgroup of patients ≤ 65 years old. Majlis et al[2] reported that patients with MCL who present with the mantle-zone histopathologic pattern have a better prognosis compared with patients who present with nodular or diffuse patterns and cited, for this group, a CR rate of 75%, with 3-year rates of progression-free survival (PFS) and OS of 83% and 100%, respectively. In contrast, patients with a diffuse histopathologic pattern had only a 20% CR rate and 3-year PFS and OS

Table 7. Cycles With Dose Reductions According to Age and Regimen

Age/Regimen	No. of Patients	No. of Cycles	Reduced Cycles		*P*
			No.	%	
Patient age					
All ages	97	602	142	24	
≤ 65 years	65	410	70	17	
> 65 years	32	192	72	38	.00001
Regimens					
R-HCVAD		302	51	17	
R-Mtx/Ara-C		300	91	30	.0002

Abbreviations: R-HCVAD, rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; R-Mtx/Ara-C, rituximab plus methotrexate and cytarabine.

rates of 26% and 55%, respectively.[2] Patients with the nodular histopathologic sybtype did not fare any better. It is for this reason that we excluded patients with the mantle-zone variant of MCL from this study. In the same study by Majlis et al,[2] the most common clinical feature of patients presenting with the mantle-zone pattern was generalized lymphadenopathy and absence of bone marrow involvement. In contrast, patients in that study whose lymph nodes showed the diffuse pattern presented most frequently with bone marrow involvement. In our current trial, 14 patients presented without lymphadenopathy and with marrow involvement at diagnosis, which makes the diagnosis of the mantle-zone variant unlikely. In addition, the 3-year FFS for these 14 patients was similar to that of patients with the diffuse or nodular histopathologic variants. Thus, we have included them in our analysis.

The overall CR/CRu rate of 87% in the current study compares favorably with that of other reported series using doxorubicin-containing therapies.[3-9,20] More recently tested chemotherapeutic combinations have also reported CR rates of more than 90%.[21-25] Indeed, a CR rate of 92% was achieved after four courses of a regimen consisting of fludarabine, mitoxantrone, and rituximab.[23] A CR rate of 70% was achieved in 20 patients in a study reported recently in abstract form using a modified rituximab plus hyper-CVAD regimen without high-dose methotrexate and cytarabine and with maintenance rituximab weekly for 4 weeks every 6 months for 2 years.[24] In another reported series and as part of a new approach to therapy, the use of front-line radiolabeled monoclonal antibody produced a CR rate of 50% before the start of CHOP.[25] This study offers exciting combinations of chemotherapy and radiotherapy with newer biologic therapies, but the number of patients accrued was small. More aggressive modalities for the initial treatment of MCL have been reported, mostly in small numbers of patients in whom a good response to first-line therapy is consolidated with high-dose chemotherapy and stem-cell transplantation. This approach has resulted in CR rates of up to 100%.[12,26-31] Variations in these regimens include the addition of rituximab, the use of total-body irradiation, and the use of different preparative chemotherapeutic regimens.

In the present study, the 3-year FFS rate of 64% for all ages after a median follow-up time of 40 months is significant, considering that the reported median FFS time for MCL is 10 to 18 months after treatment with doxorubicin-containing regimens.[5-9,20] This suggests an improvement, although the comparison is retrospective. Other recently reported doxorubicin-containing regimens have demonstrated an improvement in median FFS time to 24 months[21] and a 73% PFS rate at a median follow-up time of 22.5 months,[24] whereas the fludarabine, mitoxantrone, and rituximab regimen[23] has resulted in a 100% relapse-free survival rate but at the short median follow-up time of only 14 months. The report with radioimmunolabeled antibody followed by CHOP also had a short median follow-up time of 11+ months.[25] A formal comparison of these and other conventional therapies with the current study will require the design of prospective randomized trials.

The 3-year FFS rate of 73% for the subgroup of patients $\leq$ 65 years old after a median follow-up time of 40 months in the present study compares favorably with the rate reported after high-dose chemotherapy followed by consolidation with stem-cell transplantation (Table 8). However, a definite comparison would need to account for different pretreatment variables among patients, the chemotherapy regimen used, and the modality of radiotherapy used. Making these comparisons will also require the design of randomized prospective clinical trials.

An analysis of prognostic variables for FFS in the current study revealed that the pretreatment serum levels of β_2-microglobulin predicted for FFS both for the entire group and for the subgroup of patients more than 65 years old, but not for the subgroup of younger patients. β_2-microglobulin is the light chain of the class 1 major histocompatibility complex, and it has been associated with a worse prognosis in both indolent and aggressive lymphomas.[32,33] A more recent publication has also associated serum β_2-microglobulin levels with a shorter survival among patients with aggressive MCL who underwent autologous stem-cell transplantation as part of their initial treatment.[27] One possible reason why serum β_2-microglobulin was not a prognostic factor for FFS in our study within the subgroup of patients $\leq$ 65 years old is that the intense therapy eliminated this variable as a prognostic marker. The same argument can be used to explain why other pretreatment variables previously reported to be of prognostic significance when treating with less intense therapies lost their significance in our study. Another possible explanation for our results could be that the number of patients in each analyzed subgroup was small. In addition to β_2-microglobulin, LDH was shown in our study to be a prognostic factor for FFS. An elevated level of serum LDH is widely recognized as an important prognostic factor for aggressive lymphoma in risk models, including the IPI model.[18] Its combination with β_2-microglobulin alone has provided a powerful serologic predictive model for aggressive lymphomas as well.[32]

The presence of an IPI score of more than 2 was associated with a lower FFS rate. This is not surprising in view of the fact that several of the IPI components were important in our univariate analysis, including age and serum LDH levels. In the current trial, the blastoid cytologic variant was associated with a worse OS, although this difference was not statistically significant. This variant has been associated in the past with abnormalities in the *p53* and *p16* genes as well as other secondary cytogenetic and molecular abnormalities,[9] and patients with this variant have a worse outcome after treatment with doxorubicin-based conventional chemotherapy regimens.[10,11] One possible reason for the lack

Table 8. Reports of Therapy for Untreated Mantle-Cell Lymphoma Containing More Than 25 Patients

Reference	Regimen	Age (years)	No. of Patients	CR/CRu (%)	Outcome	Median Follow-Up Time (months)
Howard et al[11]	CHOP-R	31-69	40	48	Median PFS, 16.5 months	25
Hiddeman et al[22]	CHOP-R	NA	62	42	Median TTF, NR	NA
Wilson et al[21]	EPOCH-R	22-73	26	92	50% 2-year EFS	24
Gianni et al[26]	R-HDS–autoSCT	23-65	28	100	80% 3-year EFS	35
Khouri et al[27]	Hyper-CVAD–autoSCT	38-66	33	100	43% 5-year DFS	49
Khouri et al[12]	Hyper-CVAD–auto/alloSCT	41-65	25	100	72% 3-year EFS	25
Vandenberghe et al[28]	Chemo–autoSCT	24-70	195*	67	33% 5-year PFS†	44
Andersen et al[29]	Maxi-CHOP–autoSCT	38-65	41	89	15% 4-year FFS	33
Lefrere et al[31]	CHOP/DHAP-autoSCT	33-64	28	89	83% 3-year DFS	47
Dreyling et al[30]	CHOP/interferon	35-65	122	28	25% 3-year PFS	25
	CHOP/autoSCT			81	54% 3-year PFS	
Current trial	Hyper-CVAD-R+methotrexate-cytarabine-R	41-65	65	89	75% 3-year FFS	40
		41-80	97	88	64% 3-year FFS	40

Abbreviations: CR, complete response; CRu, complete response unconfirmed; NR, not reached; SCT, stem-cell transplantation; NA, not available; FFS, failure-free survival; PFS, progression-free survival; TTF, time to treatment failure; EFS, event-free survival; DFS, disease-free survival; Chemo, varied regimens; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R, rituximab; EPOCH-R, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; R-HDS, high-dose sequential rituximab; Hyper-CVAD, fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; DHAP, dexamethasone, high-dose cytarabine, cisplatin; auto, autologous; allo, allogeneic; Maxi, maximum.

*Fifteen percent underwent transplantation at relapse.

†Five-year PFS of 52% if received transplantation in first CR.

of statistical significance of the blastoid variant in our study might be related to the higher proliferative rate reported for this variant, which, in turn, makes it more susceptible to the high doses of methotrexate and cytarabine used in this regimen. Alternatively, the lack of statistical significance could be a result of the small number of such patients in our study. Unfortunately, because of the low number of events detected, a multivariate analysis for FFS or OS could not be performed.

In our FFS analysis, we decided not to censor those patients who underwent consolidation with stem-cell transplantation after achieving a PR to six cycles of chemotherapy with the intent of avoiding any possible selection of good-risk patients (ie, patients who achieved a CR after six cycles and did not need stem-cell transplantation). For similar reasons, we did not censor patients who developed treatment-related MDS (tMDS) or AML at the time of development of this secondary event.

There seems to be no plateau in the FFS and OS curves in the current study, both in the group as a whole and in age subgroups. This suggests that a subgroup of patients deemed to be in clinical complete remission still harbor minimal residual disease and that these patients may benefit from additional concurrent or maintenance treatment strategies. Alternatively, the follow-up of these patients over a longer time period might permit the detection of additional prognostically important pretreatment variables.

Hematologic toxicity in the current study was significant, which was expected for a regimen of such intensity, and 15% of the cycles were associated with neutropenic fever. In particular, the cycle containing high-dose methotrexate and cytarabine was associated with a higher rate of neutropenic fever and with the need for more reductions in the dose of subsequent chemotherapeutic agents; however, there was no difference in rate of neutropenic fever according to age subgroup.

The development of tMDS in three patients and AML in one patient is of concern. All three patients with tMDS in our study had diploid pretreatment cytogenetics. A recent review of tMDS/AML data estimates the risk of developing tMDS/AML after long-term treatment with alkylating agents to be 1% to 1.5% per year from 2 to 10 years after the start of primary chemotherapy.[34] Because the median follow-up of the current study was 40 months, it might be too early to conclude whether the incidence of MDS in our current trial is significantly different from that reported in the literature.

The total dose of cyclophosphamide in this regimen (5.4 to 7.2 g/m^2) was not much different when compared with the dose in eight cycles of CHOP or cyclophosphamide, vincristine, and prednisone, which is 6 to 8 g/m^2. However, the cyclophosphamide in hyper-CVAD is fractionated, and this may lead to more intense exposure of the bone marrow cells to the alkylating agent. Another possible explanation for the occurrence of tMDS in our MCL patients involves the recently reported 100-fold increase in the number of secondary malignancies observed versus expected in MCL.[35] An additional explanation for the finding of tMDS might be the systematic and more thorough evaluation for other toxicities, such as tMDS, as part of this trial in an academic setting.

In conclusion, the results of this trial show that rituximab plus hyper-CVAD alternating with rituximab plus methotrexate-cytarabine is an effective regimen for the induction of complete remissions in patients with newly diagnosed aggressive MCL and produces prolonged remissions in patients 65 years of age or younger. This is achieved at the expense of significant but expected toxicity. Because of this regimen's shorter FFS rate concurrent with significant toxicity in patients more than 65 years of age, this regimen is not recommended as standard therapy for this age subgroup. Larger prospective randomized trials are needed to define its role compared with existing treatment modalities.

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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.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
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ERRATA

The October 1, 2005, article by Romaguera et al titled, "High Rate of Durable Remissions After Treatment of Newly Diagnosed Aggressive Mantle-Cell Lymphoma With Rituximab Plus Hyper-CVAD Alternating With Rituximab Plus High-Dose Methotrexate and Cytarabine" (J Clin Oncol 23:7013-7023, 2005) contained inaccurate information in Table 4 as follows:

Whereas the overall 3-year FFS was given as 65%, it should have read 64%.

Whereas the 3-year FFS of age > 65 years (No) was given as 75%, it should have read 73%.

Whereas the *P* value for age > 65 years (No) was given as .01, it should have read .02.

Whereas the 3-year OS for age > 65 years (No) was given as 85%, it should have read 86%.

Whereas the 3-year OS for age > 65 years (Yes) was given as 75%, it should have read 74%.

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The November 20, 2005, article by Carli et al titled, "Pediatric Malignant Peripheral Nerve Sheath Tumor: The Italian and German Soft Tissue Sarcoma Cooperative Group" (J Clin Oncol 23:8422-8430, 2005) contained inaccurate information.

The spelling of the tenth co-author's name was given as Eura Koscielniak, whereas it should have read Ewa Koscielniak. The Authors' Disclosure of Potential Conflicts of Interest section should have contained the following statement: "The authors indicated no potential conflicts of interest."

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The December 1, 2005, article by Burtness et al titled, "Phase III Randomized Trial of Cisplatin Plus Placebo Compared With Cisplatin Plus Cetuximab in Metastatic/Recurrent Head and Neck Cancer: An Eastern Cooperative Oncology Group Study" (J Clin Oncol 23:8646-8654, 2005) contained incorrect information.

In the Abstract, in the second-to-last sentence of the Results section, the values for objective response rate were interchanged. Whereas 10% was given for arm A and 26% for arm B, it should have read 26% for arm A and 10% for arm B.

In Figure 1, the median values were interchanged. Whereas 2.7 was given for the C225 arm and 4.2 for the placebo arm, it should have read 4.2 for the C225 arm and 2.7 for the placebo arm.

In Figure 2, the median values were interchanged. Whereas 8 was given for the C225 arm and 9.2 for the placebo arm, it should have read 9.2 for the C225 arm and 8 for the placebo arm.

The online version has been corrected in departure from the print.

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