Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network

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Received 24 April 2006; accepted 26 April 2006

Background: There is no standard first line treatment for mantle cell lymphoma.

Patients and methods: This was a multicenter phase II pilot study of rituximab and modified hyper-fractionated cyclophosphamide, vincristine doxorubicin, dexamethasone (modified R-hyperCVAD) administered every 28 days for four to six cycles followed by rituximab maintenance therapy consisting of four weekly doses every 6 months for 2 years. Unlike traditional hyperCVAD regimens, no methotrexate or cytarabine was administered.

Results: Of 22 patients, the overall response rate was 77% and the complete response rate was 64%. With a median follow-up time of 37 months in surviving patients, the median PFS was 37 months and the median OS was not reached. The achievement of a molecular remission did not correlate with improved outcome. The major toxicity was expected myelosuppression. Two patients died during induction treatment. There were no major adverse effects during maintenance therapy.

Conclusion: In a multicenter trial, modified R-hyperCVAD was tolerable and effective induction therapy for untreated MCL. Maintenance rituximab appeared to prolong PFS without increasing toxicity.

Key words: mantle cell lymphoma, chemotherapy, biologic therapy

Introduction

Mantle cell lymphoma (MCL) comprises approximately 6%–8% of newly diagnosed non-Hodgkin’s lymphomas and is a particularly challenging lymphoma subtype to manage, with many reports indicating a median survival of 3–4 years [1–4]. It had the poorest 5-year survival of all the non-Hodgkin’s lymphoma subtypes in the NHL classification project and is considered incurable with standard therapies [5]. High response rates are seen with CHOP plus rituximab (R), but the progression-free survival (PFS) is disappointingly short (median 16–20 months) [6, 7]. Some phase II studies and registry studies have suggested a benefit for selected patients using autologous stem cell transplantation (ASCT) consolidation in first remission [8–12]. However, many patients are not transplant eligible and this strategy did not prolong overall survival in a randomized clinical trial [13]. Very favorable results have been reported for a regimen consisting of R-hyperCVAD alternating with rituximab plus methotrexate and cytarabine (R-Mtx/AraC) [14]. This regimen can be prohibitively toxic for patients over the age of 65 and younger patients with co-morbid illness. Since the median age for newly diagnosed mantle cell lymphoma patients is 64, approaches that do not include stem cell transplantation or involve highly aggressive chemotherapy regimens need to be developed. With this idea in mind, we devised a modified version of R-hyperCVAD with rituximab maintenance to test in a phase II pilot study.

This study explored two different hypotheses. First, we hypothesized that eliminating methotrexate and cytarabine (R) from the induction hyperCVAD regimen would result in high complete response rates with acceptable toxicity. Secondly, we hypothesized that adding rituximab maintenance would prolong the PFS without increasing toxicity.

Patient and methods

Patient eligibility

This was a prospective study performed in the Wisconsin Oncology Network, an affiliation between the University of Wisconsin Comprehensive Cancer Center and the University of Wisconsin System. Patients were eligible if they had the following criteria: (a) histologically confirmed primary or secondary MCL; (b) measurable disease; (c) age 18 or older; (d) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (e) a life expectancy of at least 6 months; (f) adequate hematologic, renal, and hepatic function; (g) prior therapies for MCL had to be completed at least 4 weeks prior to study entry; (h) prior therapeutic stem cell transplantation (ASCT) as part of MCL therapy was permitted; and (i) patients could not be enrolled if they had received prior rituximab therapy. Patients were excluded if they had any of the following: (a) prior treatment with hyperCVAD chemotherapy; (b) the presence of any significant concomitant medical conditions that would interfere with the patient’s ability to participate in the study or to receive the planned study treatment; (c) prior or concurrent chemotherapy or hematopoietic stem cell transplant (HSCT) for any malignancy (other than MCL); (d) prior or concurrent radiotherapy to greater than 20% of the bone marrow; (e) prior or concurrent investigational agent; and (f) the presence of any other malignancy (other than non-melanoma skin cancer or basal cell carcinoma).
Cancer Center and several community-based practices. Eligible patients must have had untreated MCL confirmed by a central hematopathologist. Eligibility criteria included the following: at least 18 years of age, an ECOG performance status of 0–2, an absolute neutrophil count of 21500/µl platelet count 2100 000/µl (unless the cytopenia was caused by marrow infiltration of lymphoma or splenomegaly), a serum creatinine level of ≤2 mg/dl, a serum bilirubin of ≤1.5 mg/dl and an AST ≤2.5 times the upper limit of normal. Patients were ineligible if they were pregnant or lactating, had an active second malignancy, an uncontrolled infection, CNS lymphoma, HIV, New York Heart Classification III or IV disease, or were incapable of giving informed consent. The University of Wisconsin Human Subjects Committee and the local institutional review boards of participating sites approved this trial.

### Treatment Schedule: Modified R-hyperCVAD

The treatment schema is depicted in Figure 1. Rituximab 375 mg/m² was administered on day 1 of all treatment cycles except cycle 1, due to concern of excessive infusion reactions in patients with high circulating lymphocyte counts. Following completion of the rituximab infusion, chemotherapy was initiated: cyclophosphamide 300 mg/m² was administered intravenously over 3 h, every 12 h days 1–3 (six doses, total dose 1800 mg/m²), doxorubicin 25 mg/m²/day was administered as a continuous intravenous infusion over 48 h on days 1–2 (total dose 50 mg/m²), vincristine 2 mg i.v. push was administered on day 3, and dexamethasone 40 mg orally was given on days 1–4. The first five patients also received vincristine 2 mg i.v. push on day 11 and dexamethasone 40 mg orally on days 11–14. All patients received filgrastim 5 µg/kg/day subcutaneously beginning on day 5 and continuing until the absolute neutrophil count was greater than 4000/µm³. Cycles were repeated every 28 days. Patients were treated until they achieved a complete response plus two additional cycles, up to a maximum of six cycles. Supportive care measures included allopurinol 300 mg administered orally daily for the first cycle of therapy, acetaminophen 650 mg orally and diphenhydramine 50 mg orally prior to all rituximab doses, and acetaminophen 650 mg orally and dexamethasone 40 mg orally on days 11–14. All patients received trimethoprim/sulfamethoxizole 160/800 mg administered orally twice daily on either Saturday/Sunday or Monday/Wednesday/Friday.

### Treatment Schedule: Maintenance Rituximab

Patients achieving a PR or CR/CRu after modified R-hyper CVAD received rituximab 375 mg/m² given weekly for 4 consecutive weeks, repeated every 6 months for a total of four courses. Maintenance rituximab began 6 months after completing chemotherapy. Patients with progressive disease at any point came off study treatment.

### Patient Evaluation and Response Criteria

Disease restaging occurred after each even numbered modified R-hyperCVAD cycle, every 3 months while on maintenance therapy, and every 6 months following the completion of maintenance therapy. Restaging included a physical examination, all routine blood tests, CT scans of the chest/abdomen/pelvis and a bone marrow evaluation if assessing for a complete response (CR). Response criteria were according to the International Workshop to Standardize Response Criteria for non-Hodgkin’s Lymphoma [15].

### Correlative Studies for Molecular Response

Analysis for B-cell clonality was performed at baseline, at completion of induction therapy and every 6 months while on maintenance therapy. Blood and bone marrow was collected in EDTA and then the lymphocyte fraction was isolated by Ficoll–Hypaque gradient centrifugation by routine methods. The DNA was extracted from the lymphocytes using QIAamp DNA Blood Kit (QIAGen Inc, Valencia, CA) and/or by PCR with a consensus FR3 primer and PAGE separation as previously described [17]. Amplicon length of clonal bands seen on subsequent samples was compared with previous analyses. Pretreatment specimens were also screened for t(11;14) translocation by PCR as previously described [18]. Patients whose t(11;14) translocations were detectable by PCR were monitored by this method as well.

### Statistical Methods

The primary end point of this phase II pilot study was complete response (CR) rate. The sample size determination was based upon precision, defined by the lower limit of a one-sided 90% confidence interval. Using a sample size of 20 eligible patients, an observed CR rate of 60% or more would provide preliminary information that this treatment regimen was worthy of further study. Secondary end points included estimates of molecular response rates, overall response rate, progression-free survival (PFS) and overall survival (OS). All response rate estimates were reported with 90% confidence intervals, and PFS and OS were estimated by the Kaplan–Meier product limit method [19].

### Figure 1. Treatment schema for modified R-hyperCVAD with rituximab maintenance.
results

clinical characteristics

Between October 2000 and March 2004, 22 patients with untreated MCL were enrolled into the study. Table 1 lists the baseline characteristics of the patients. The median age was 63 (range 40–81). Most patients had an ECOG performance status of 0 or 1. Twenty of 22 (91%) patients were male, and 19/22 (86%) had stage IV disease. Applying the international prognostic index for diffuse aggressive lymphomas, 14% patients were low risk, 27% were low-intermediate, 27% were high-intermediate and 32% were high risk. An elevated LDH was noted in 41% and an elevated beta 2 microglobulin was noted in 86%. Most patients had a nodal presentation while two patients had a leukemic presentation with massive splenomegaly.

response

Response was assessed every two cycles during the modified R-hyperCVAD induction and every 3 months during R maintenance. The data are summarized in Table 2. Two patients expired before any response assessment and were considered non-responders. Three patients experienced progressive disease (PD) during induction therapy, including both patients with leukemic presentations. The remaining 17 patients responded to the R-hyperCVAD induction (14 CR and three PR) for an ORR of 77% (90% CI 58% to 91%) and CRR of 64% (90% CI 44% to 80%). Four patients achieved CR after two cycles of therapy and received four total cycles, while the remaining 13 patients received six total cycles. Of the three patients entering maintenance rituximab in PR, none have improved their response category to date.

PFS and OS

With a median follow-up of 37 months in surviving patients, the median PFS is 37 months (90% CI 15.5 months to not reached) and the median OS has not been reached yet (Figure 2). The PFS and OS rates at 2 years are 59% (90% CI 40% to 77%) and 77% (90% CI 56% to 90%), respectively. One patient progressed before the initiation of maintenance rituximab, and three patients progressed during maintenance rituximab. Two of the three patients entering maintenance in PR progressed during treatment, while only one of 13 patients entering maintenance in CR progressed during treatment.

![Figure 2. Kaplan–Meier estimates for PFS and OS. Median follow up is 37 months (range 22–62 months). (A) Median PFS is 37 months. (B) Median OS is not reached.](https://academic.oup.com/annonc/article-abstract/17/9/1418/214615)
Four patients in CR relapsed 6–12 months after completing maintenance rituximab.

**molecular responses**
Molecular responses for the 15 patients with sufficient data are shown in Figure 3. Nine of 15 patients achieved molecular remissions after induction therapy, with five of those nine maintaining molecular remission through maintenance. One patient achieved molecular remission after induction therapy, but progressed prior to the initiation of maintenance therapy. Two additional patients converted to molecular remission during maintenance therapy. A comparison of patients achieving molecular remission at their last monitored time point \((n = 8)\) with patients not in molecular remission at their last monitored time point \((n = 7)\), revealed no correlation with PFS.

**toxicity**
The major toxicity, as expected, was myelosuppression. A summary of toxicities is listed in Table 3. Grade 3–4 neutropenia was almost universal despite routine administration of filgrastim. There were two toxic deaths among the first five patients enrolled in the study, leading to a temporary suspension of the protocol and analysis of the events. The first death, a result of pseudomonas sepsis, occurred in a 67-year-old woman after cycle 2. The second death occurred in a 72-year-old man who developed peritonitis on day 12 of cycle 1. In reviewing the two deaths, we were concerned that the day 11–14 dexamethasone may have masked signs and symptoms of infection, delaying appropriate treatment. This phenomenon has been reported in the pediatric literature, leading to the removal of mid-cycle dexamethasone from some pediatric ALL protocols [20]. We decided to resume the trial with omission of the day 11 vincristine and the day 11–14 dexamethasone. The remaining 17 patients enrolled experienced no unexpected toxicities during the modified R-hyperCVAD induction. During the 2 years of rituximab maintenance, no grade 4 toxicities and only five incidences of grade 3 toxicity were noted. One patient developed delayed neutropenia, which responded promptly to filgrastim. No significant infections were observed.

**discussion**
This study explored two different hypotheses. First, we hypothesized that eliminating methotrexate and cytarabine while adding rituximab to the induction hyperCVAD would result in high complete response rates with acceptable toxicity. We observed a CR rate of 64% and after a protocol modification we observed an acceptable toxicity profile. Secondly, we hypothesized that adding maintenance rituximab would prolong the PFS without increasing toxicity. The median PFS of 37 months is promising and may reflect the added benefit of maintenance rituximab.

**Table 3. Adverse events during induction therapy**

<table>
<thead>
<tr>
<th>Event</th>
<th>Total no. grade 3 events</th>
<th>Total no. grade 4 events</th>
<th>Total no. grade 5 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
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<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection w/ neutropenia</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>2</td>
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</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>1</td>
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</tr>
<tr>
<td>Neuropathy</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
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<td>0</td>
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</tr>
<tr>
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</tr>
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</tr>
<tr>
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<tr>
<td>Colonic perforation</td>
<td>0</td>
<td>0</td>
<td>1</td>
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Common Toxicity Criteria version 2.0.
made other changes to the R-hyperCVAD regimen in an effort to reduce toxicity. These modifications included repeating cycles every 28 days rather than every 21 days, elimination of day 11 vincristine, elimination of day 11–14 dexamethasone, and administration of a concurrent rather than a sequential 48-h doxorubicin infusion, resulting in a CHOP-like regimen. Whether it is superior to R-CHOP is unknown but we do note a CR rate of 64%, which is higher than CR rates reported in trials utilizing R-CHOP (34% and 48%) [6, 7]. Furthermore, our data suggests that achieving CR before maintenance rituximab is an important goal. Achieving CR was also shown to be an important end point in studies evaluating the role of autologous stem cell transplantation (ASCT) in first remission [9, 21].

Autologous stem cell transplantation in first remission is commonly practiced and there are several reports suggesting benefit with EFS near 70% at 3 years [8–12]. Other transplant studies have reported less promising results [21, 22]. A limitation to this strategy is the exclusion of approximately one-half of newly diagnosed patients, due to age considerations or co-morbid illness. The lone randomized clinical trial (RCT) examining the role of upfront ASCT has been reported by the European MCL Network [13]. This study demonstrated a significant PFS benefit for ASCT compared with IFN-α (median 39 months versus 17 months) but has not proven an OS benefit to date.

The application of maintenance rituximab after first-line chemoimmunotherapy has not been previously reported in MCL. The current study suggests that 2 years of rituximab maintenance after a moderately aggressive chemoimmunotherapy ‘induction’ prolongs PFS in previously untreated MCL. The median PFS of 37 months reported here is substantially longer than noted in other studies using regimens of similar intensity. For example, a recently published trial examining the utility of R-CHOP therapy in MCL reported median EFS of 21 months while a phase II study from the Dana Farber Cancer Institute reported a median PFS of only 16.6 months [6, 7]. We cannot be certain that the PFS results we observed is a function of maintenance rituximab and it is possible that similar results would have been obtained with the induction chemoimmunotherapy alone. However, the pattern of relapse suggests benefit from maintenance rituximab. Of the patients achieving CR to induction therapy, we observed only one relapse during maintenance therapy but four relapses 6–12 months after completing maintenance rituximab.

The notion that maintenance rituximab confers clinical benefit has been demonstrated by three RCTs in other NHL subtypes. A RCT performed by the Eastern Cooperative Oncology Group (E1496) demonstrated a major PFS benefit when 2 years of maintenance rituximab was given after CVP chemotherapy in previously untreated low-grade lymphoma [23]. E1496 also suggests a survival advantage for maintenance rituximab in the follicular lymphoma subset [24]. A RCT conducted by the European Organization for Research and Treatment of Cancer (EORTC) in relapsed follicular lymphoma also demonstrated a major PFS benefit for 2 years of maintenance rituximab after either CHOP or R-CHOP therapy, and strongly suggests an overall survival benefit [25]. Finally, a RCT conducted by the German Low Grade Lymphoma Study Group (GLSG) compared 1 year of maintenance rituximab with observation in patients with relapsed follicular and relapsed MCL. Consistent with other reports, a major PFS benefit was noted in both follicular and in MCL subtypes, and there is a suggestion of an overall survival benefit [26].

Not all studies examining the role of maintenance therapy have demonstrated benefit. A randomized study evaluating the role of maintenance rituximab in MCL was conducted by the Swiss Group for Clinical Cancer Research (SAKK) [27]. Most of patients in the study were previously treated although about one-third were treatment-naive. Induction treatment consisted of single-agent rituximab, which produced an OR rate of 27% and a CR rate of 2%. The maintenance schedule used in the trial, a single dose administered every 8 weeks times four, did not improve response rates or response duration. There are at least three possible explanations for these findings. First, it is possible that maintenance rituximab truly has no role in the treatment of MCL. Secondly, it is possible that the dose and schedule of maintenance rituximab is important. The SAKK trial used fewer doses (4 versus 8–16) and administered them over a shorter period of time (8 months versus 24 months) compared with other maintenance rituximab studies. Thirdly, it is possible that remission status (CR versus PR versus SD) is an important factor determining the benefit of maintenance rituximab. For example, E1496 demonstrates the largest benefit for maintenance rituximab in those patients who achieve a state of minimal residual disease after CVP induction. Since the single-agent rituximab induction in the SAKK study generated responses in only 27% and CRs in only 2%, the benefits of maintenance therapy may have been lost because of a less effective induction regimen. Consistent with this hypothesis, in the current study we noted PD during maintenance therapy in two of three patients entering maintenance in PR compared with one of 13 patients entering maintenance in CR.

The current study suggests a prolongation in PFS for untreated MCL by the application of maintenance rituximab for 2 years following the completion of a moderately aggressive chemoimmunotherapy regimen. The major weakness of the current study is the small sample size. Strengths include the multi-center nature of the trial, including community oncology sites, and the inclusion of a representative mantle cell population (median age 63). Despite an older cohort, the median PFS observed in the current study was similar to that observed in a RCT which employed ASCT as consolidation (37 months versus 39 months) [13]. Whether maintenance rituximab could replace or enhance ASCT as a consolidation step should be a focus of future study. While the current study provides a signal for extended remission with the use of maintenance rituximab, there remains much room for improvement. One attractive strategy is the incorporation of bortezomib, an agent with significant activity in relapsed MCL, into the induction regimen [28, 29]. Other strategies to improve the current regimen could include a dose intensification to 21-day cycles, standardization to six induction cycles for all patients, and the prolongation of maintenance rituximab beyond 2 years. Such a regimen is currently being tested for safety at the University of Wisconsin, and will be tested for efficacy in a phase II trial of the Eastern Cooperative Oncology Group.
Acknowledgements

This clinical trial was designed at the AACR/ASCO Methods in Clinical Cancer Research Workshop. Special thanks to Gina Petroni who assisted in the study design and made helpful comments on the manuscript. The research was supported by UWCCC core grant 5 P30 CA014520–33 and Genentech BioOncology. BSK was supported by Clinical Research Scholar Award 1 K12 RR 01614–01.

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