Combination of rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil (RiPAD+C) as first-line therapy for elderly mantle cell lymphoma patients: results of a phase II trial from the GOELAMS


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Background: There is no consensual first-line chemotherapy for elderly patients with mantle cell lymphoma (MCL). The GOELAMS (Groupe Ouest-Est des Leucémies Aiguës et Maladies du Sang) group previously developed the (R)VAD+C regimen (rituximab, vincristine, doxorubicin, dexamethasone and chlorambucil), which appeared as efficient as R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone) while less toxic. Based on this protocol, we now added bortezomib (RiPAD+C: rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil) given its efficacy in relapsed/refractory MCL patients. The goal of the current phase II trial was to evaluate the feasibility and efficacy of the RiPAD+C regimen as frontline therapy for elderly patients with MCL.

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Patients and methods: Patients between 65 and 80 years of age with newly diagnosed MCL received up to six cycles of RiPAD+C.

Results: Thirty-nine patients were enrolled. Median age was 72 years (65–80). After four cycles of RiPAD+C, the overall response rate was 79%, including 51% complete responses (CRs). After six cycles, CR rate increased up to 59%. After a 27-month follow-up, median progression-free survival (PFS) is 26 months and median overall survival has not been reached. Four patients (10%) discontinued the treatment because of a severe toxicity and seven patients (18%) experienced grade 3 neurotoxicity.

Conclusion: The bortezomib-containing RiPAD+C regimen results in high CR rates and prolonged PFS with predictable and manageable toxic effects in elderly patients with MCL.

Key words: bortezomib, elderly, lymphoma, mantle cell, rituximab

Introduction

Mantle cell lymphoma (MCL) represents a distinct histological subtype of malignant B-cell neoplasia [1]. It is typically a disease of the elderly (median age 68 years) with a higher incidence in men [2]. The majority of patients (>70%) present with advanced-stage disease (Ann Arbor III/IV) at initial diagnosis. MCL is also characterized by a clinically aggressive behavior. For patients who cannot receive intensive therapy followed or not by autologous stem-cell transplantation, typically elderly patients, the median survival is ~3–4 years [2].

There is currently no consensual first-line therapy for elderly MCL patients. These patients do not benefit from dose-intensive chemotherapy up front [3]. Despite unproven superiority of anthracycline-containing regimens, treatments based on CHOP (combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone) are commonly used. With such treatments, in combination or not with rituximab, the outcome of patients is generally poor with a median progression-free survival (PFS) ranging between 16 and 21 months, with no significant difference between protocols [4–6]. Regimens comprising high-dose cytarabine such as DHAP (cisplatin, cytarabine, dexamethasone) [7] or hyper-CVAD [8] have been shown to achieve better responses but their toxicity limits their use in elderly patients.

The GOELAMS (Groupe Ouest-Est des Leucémies Aigües et Maladies du Sang) group recently demonstrated that VAD+C (vincristine, doxorubicin, dexamethasone, chlorambucil), a CHOP-like regimen comprising continuous infusion of anthracycline and sequential administration of chlorambucil as alkylating agent, had an efficacy comparable with R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone) with a much lower toxicity [4]. Additionally, it has been shown that the proteasome inhibitor bortezomib (Velcade®) has efficacy in relapsed/refractory MCL patients [9, 10]. These results prompted the GOELAMS group to conduct a phase II prospective clinical trial evaluating the bortezomib-containing RiPAD+C regimen as a first-line therapy for elderly MCL patients. This regimen is similar to VAD+C with addition of rituximab and replacement of vincristine by bortezomib. In this article, we report the final results of this study that aimed to evaluate the efficacy and safety of the RiPAD+C regimen. The prognostic value of the recently described GOELAMS index in this elderly population was also evaluated and compared with the standard Mantle Cell Lymphoma International Prognostic Index (MIPI) and MIPIb scores.

Patients and methods

Study design

The present study is a prospective, nonrandomized, multicenter phase II trial that was designed to assess the safety and efficacy of the RiPAD+C regimen in elderly patients with newly diagnosed MCL. The study was registered at http://www.clinicaltrials.gov under, NCT00740415.

Inclusion criteria

Patients were required to have histologically confirmed MCL according to the World Health Organization classification (including blastoid forms); Ann Arbor stage II–IV disease; no prior treatment; age between 65 and 80 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) between zero and two as well as adequate renal, cardiac and hepatic functions. Patients were excluded if they had infection with human immunodeficiency, hepatitis B or hepatitis C virus. All histological samples were centrally reviewed and Ki67 expression was evaluated by the referent pathologist of the trial as previously described [4] according to the European guidelines [11]. All patients were required to sign a written informed consent approved by the institutional review board in accordance with the Declaration of Helsinki.

Treatment schedule

Following baseline evaluation, patients received up to six cycles of the RiPAD+C regimen (supplemental Figure S1, available at Annals of Oncology online): rituximab 375 mg/m² on day 1 (and day 8 of cycle 1); bortezomib (PS-341; Velcade®) 1.3 mg/m² on days 1, 4, 8 and 11; doxorubicin 9 mg/m²/day as a continuous infusion from day 1 to 4; dexamethasone 20 mg twice daily from day 1 to 4; chlorambucil 12 mg/day from day 20 to 29. Cycles were repeated every 35 days. After four cycles, responding patients [complete response (CR) or partial response (PR)] received two additional cycles for a maximum of six. Patients did not receive any maintenance therapy.

Dose modifications

In case of severe (grade 3) hematologic toxicity consisting in neutropenia and/or thrombocytopenia, administration of bortezomib and chlorambucil was delayed and the dose was reduced according to the trial’s guidelines (supplemental Tables S1 and S2, available at Annals of Oncology online). In case of grade 2 neurologic toxicity, bortezomib administration was reduced accordingly (supplemental Table S3, available at Annals of Oncology online). Growth factors were used at the discretion of the physicians.

Efficacy and safety assessments

Disease response, defined as CR, unconfirmed complete response (CRu), PR, stable disease (SD) or progressive disease (PD), was assessed according to the International Workshop Response Criteria [12]. Tumor assessments
were carried out on all target lesions identified clinically and by computed tomographic scans (thorax, abdomen and pelvis) at baseline, after four cycles, at the end of treatment, every 3 months during the six following months and every 6 months thereafter until year 3. Treatment efficacy was also assessed by measuring the PFS and the overall survival (OS) for each patient. Duration of PFS was calculated from the date of registration on to the study to the date of documented relapse, disease progression or death from any cause [12]. Duration of OS was calculated from the date of registration on to the study to the date of death from any cause [12].

Adverse events were monitored throughout and toxic effects assessed by the National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3.0.

**statistical methods**
The primary end point of the study was the overall response (OR) rate (CR + CRu + PR) after four cycles of RiPAD+C. The secondary end points were OR rate after six cycles, PFS, OS and toxic effects. Kaplan–Meier survival curves and log-rank test were used to estimate PFS and OS and the prognostic value of different scores (MIPI, MIPIb and GOELAMS index). The GOELAMS index, which integrates four independent factors [Ki67 > 26%, ECOG of more than one, B symptoms and lactate dehydrogenase (LDH) > normal], the MIPI and MIPIb scores were calculated as previously described [4, 13].

**results**

**patients**
From June 2007 to December 2008, 39 patients were enrolled in this phase II trial. Baseline characteristics of the patients are summarized in Table 1. The median age at diagnosis was 72 years (65–80). All patients had disseminated stage III or IV disease and 25% had B symptoms. Eleven (30%) patients presented with a blastoid variant. Ki67 staining was superior to prognostic value of different scores (MIPI, MIPIb and GOELAMS index). The GOELAMS index, which integrates four independent factors [Ki67 > 26%, ECOG of more than one, B symptoms and lactate dehydrogenase (LDH) > normal], the MIPI and MIPIb scores were calculated as previously described [4, 13].

**safety**
A total of 195 courses of chemotherapy were delivered. Among these, toxicity was assessed for 189 (97%). The remaining courses (3%) were not evaluated for toxicity because of missing data. The toxic effects most frequently observed are listed in Table 2. Treatment-associated grade 3 and 4 adverse events predominantly comprised myelosuppression (leukocytopenia, thrombocytopenia and anemia), infection, lung toxicity and peripheral neuropathy. Twelve patients (34%) required hospitalization [median duration: 7 days (1 and 55)] during the course of treatment. Nine patients (24%) required transfusions. Seven patients (18%) experienced grade 3 peripheral neuropathy. Four patients (10%) prematurely discontinued the treatment because of toxicity. Two patients died of severe sepsis. The first patient experienced bacterial and fungal infection while neutropenic after the second cycle of RiPAD+C. He was considered in partial remission at the time of death (Figure 1). The second patient experienced yeast infection after the fourth cycle of RiPAD+C. His absolute neutrophil count was normal and he was considered in PR at the time of sepsis.

**efficacy**
Thirty-two of the 39 patients (82%) received the first four cycles of RiPAD+C. His absolute neutrophil count was normal and he was considered in PR at the time of sepsis.
With a median follow-up of 27 months, 27 patients (70%) remain alive. Two patients died of severe sepsis and 10 because of disease progression. The median PFS is 26 months and the median OS has not been reached (Figure 2A and C). OS and PFS were significantly better for patients in CR or CRu at final evaluation compared with other patients (Figure 2B and D).

We also evaluated the prognostic value of the MIPI, MIPIb and GOELAMS index in this cohort of elderly MCL patients treated with the RiPAD+C regimen (Figure 3). PFS and OS statistically correlated with the GOELAMS index (Figure 3A and B). In contrast, neither the MIPI nor the MIPIb stratified patients for survival (Figure 3C–F).

**discussion**

The goal of the current trial was to evaluate the feasibility and efficacy of a new bortezomib-containing regimen as frontline therapy for elderly patients with MCL. MCL is typically a disease of the elderly. Only regimens comprising high-dose cytarabine have shown improved response rates but their toxicity limits their use in elderly patients. Other regimens, including R-CHOP, are rather disappointing and do not provide long-term control of the disease. We previously developed the (R)VAD+C (rituximab, vincristine, doxorubicin, dexamethasone and chlorambucil) regimen that is as efficient as R-CHOP while less toxic and thus appears particularly well fitted for elderly patients [4]. Based on this protocol, we now added bortezomib to enhance its efficacy (RiPAD+C). Thirty-nine previously untreated patients were enrolled in this prospective phase II trial to receive the bortezomib-containing RiPAD+C regimen up front.

In terms of toxicity, the RiPAD+C regimen appeared to be fairly well tolerated in this population of elderly patients. Only four patients had to prematurely discontinue the treatment because of toxicity. Myelosuppression was manageable with only 8% febrile neutropenia. As expected, despite the withdrawal of vincristine, the use of bortezomib induced a significant percentage of neurotoxicity. In our cohort, peripheral neuropathy occurred in 45% of patients including CR or CRu at final evaluation compared with other patients (Figure 2B and D).

CR, complete response; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

**Table 2. Toxic effects**

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>Grade 3</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Hematologic (N = 39)</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>26</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19</td>
<td>49</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>72</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Non-hematologic (N = 38*)</td>
<td>38*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infectionb</td>
<td>17</td>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>7</td>
<td>18</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Kidney</td>
<td>10</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>18</td>
<td>47</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>GI</td>
<td>18</td>
<td>47</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Liver</td>
<td>9</td>
<td>24</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>11</td>
<td>29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>17</td>
<td>45</td>
<td>7</td>
<td>18</td>
</tr>
</tbody>
</table>

*One patient in progression after cycle 1, not evaluated for toxicity.
*Two patients died of severe sepsis.

GI, gastrointestinal.

**Figure 1.** CONSORT diagram of patients undergoing treatment with RiPAD+C. CONSORT, Consolidated Standards of Reporting Trials; RiPAD+C, rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil.

**Table 3. Response to treatment**

<table>
<thead>
<tr>
<th></th>
<th>Interim (four cycles)</th>
<th>Final (six cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (N = 39) %</td>
<td>No. of patients (N = 39) %</td>
</tr>
<tr>
<td>CR/CRu + PR</td>
<td>31 79 29</td>
<td>74</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>20 51 23</td>
<td>59</td>
</tr>
<tr>
<td>PR</td>
<td>11 28 6</td>
<td>15</td>
</tr>
<tr>
<td>SD/PD</td>
<td>8 21 10</td>
<td>26</td>
</tr>
</tbody>
</table>

CR, complete response; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.
18% of grade 3 neuropathy. These results are significantly higher than what has been observed with R-CHOP, which induced neurotoxicity in 35% of patients with only 1% of grade 3–4 neuropathy [6]. However, the incidence and severity of neuropathy with our biweekly schedule of bortezomib was comparable with that described by the Groupe d’Etude des Lymphomes de l’Adulte in combination with R-CHOP (20% incidence of grade 3 neuropathy) [14]. Still, it appears slightly superior to the 13% grade 3 peripheral neuropathy previously described in relapsed or refractory MCL patients treated with bortezomib in the Pinnacle study [9]. In the future, such neurotoxicity may be decreased by the use of s.c. rather than i.v. administration of bortezomib as recently reported by Moreau et al. [15].

In terms of efficacy, the OR rate after six cycles of RiPAD+C was 74% in intent-to-treat analysis. Compared with R-CHOP [5, 6], the RiPAD+C regimen induced a higher CR rate (60% versus 34%–48%) and prolonged PFS (26 versus 16–21 months) [5, 6]. This suggests that the quality of response after RiPAD+C may be better than after R-CHOP. The apparent superiority of the RiPAD+C regimen is further supported by the fact that the current study enrolled elderly patients (median age 72 years) presenting with poor prognostic factors [high proportion of blastoid variants (30%), elevated Ki67 (37%) and LDH (47%) and high- to intermediate-risk MIPI (98%)]. In contrast, the studies by Lenz et al. and Howard et al. enrolled a majority of young patients [median age of 61 years (61% <65 years) for Lenz et al. and 55 years for Howard et al.] with good MIPI scores (69% of low or low- to intermediate-risk MIPI for Lenz et al.). Additionally, 23% of patients from the Lenz series underwent intensive chemotherapy followed by autologous stem-cell transplantation. The results of the RiPAD+C regimen may also be compared with the previously described (R)VAD+C regimen [4]. In this latter study, 35 elderly (>60 years) patients with newly diagnosed MCL received up to eight cycles of VAD+C. The responses after four cycles were comparable between the VAD+C and the RiPAD+C regimens with 77% versus 79% OR rates and 48% versus 51% CR rates, respectively. However, the patients in the RiPAD+C group had more aggressive diseases with almost twice as many blastoid subtypes (30% versus 18%). In spite of these differences, the PFS appeared significantly longer with RiPAD+C compared with VAD+C (26 versus 16 months, respectively). This may suggest that the bortezomib-containing regimen increases the quality of the responses compared with the VAD+C regimen. In light of these results, the addition of bortezomib in the first-line regimen of MCL patients appears promising. The use of bortezomib in first-line therapy for MCL (n = 32) has been recently reported in combination with R-CHOP and showed comparable efficacy (CR: 72%, median PFS: 23 months) [16]. An international, randomized phase III clinical trial is ongoing to assess the superiority of a bortezomib-based regimen (VcR-CAP: rituximab, cyclophosphamide, doxorubicin, Velcade® and prednisone) over R-CHOP for newly diagnosed MCL patients (NCT00722137).

Our study also evaluated several prognostic scores in this population of elderly MCL patients. Prognostic factors in MCL remain a matter of debate, particularly the value of Ki67. The MIPI score has been developed to predict survival in young and elderly MCL patients. Its prognostic value has been recently confirmed in young patients treated with aggressive chemotherapy followed by autologous stem-cell transplantation.
We recently developed the GOELAMS index that integrates serum LDH level, Ki67 expression, B symptoms and ECOG PS [4]. In the current study, the GOELAMS index identified a group of elderly MCL patients with better prognosis. Forty percent of the patients (15 of 38) treated with the RiPAD+C regimen had a low GOELAMS index score conferring them with a good prognosis (median PFS not reached). Neither the MIPI nor the MIPIb identified such a group with favorable prognosis in our cohort. By contrast, Ruan et al. [16] reported that the MIPI was efficient at discriminating prognostic groups within MCL patients treated with R-CHOP plus bortezomib. This difference may be due to a lower median age in Ruan’s cohort (66 versus 72 years in our cohort) or to the limited number of patients in both studies. In the future, prognostic groups in MCL lymphoma might be better defined by including other parameters such as 18F-fluorodeoxyglucose–positron emission tomography uptake at diagnosis [18] and the recently described expression of Sox11 [19].

In conclusion, our study demonstrates that the RiPAD+C regimen can be safely administered upfront to elderly patients with MCL. Most importantly, this regimen appears capable of inducing high CR rates resulting in prolonged PFS even in patients with adverse prognostic factors. Thus, the bortezomib-containing RiPAD+C regimen represents a promising therapeutic option as frontline therapy for elderly MCL patients.

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**disclosure**

RG was the principal investigator and takes primary responsibility for the paper. RH and RG wrote the paper. SLG, MOU, CM, SC, CD, KB, MAV, MPM, OT, NA, PR, AHEY, LS, LF, DA, JLH and HM recruited the patients. SCM carried out the laboratory work for this study. The authors reported no potential conflicts of interest.

**references**