

# Comparative Outcomes Following CP-R, CVP-R, and CHOP-R in Waldenström's Macroglobulinemia

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## Abstract

Since the adoption of rituximab, the importance of doxorubicin and vincristine as treatment components remains to be clarified in Waldenström's macroglobulinemia (WM). We therefore examined the outcomes of symptomatic patients with WM who received CHOP-R (cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab; n = 23), CVP-R (cyclophosphamide/vincristine/prednisone plus rituximab; n = 16), or CP-R (cyclophosphamide/prednisone plus rituximab; n = 19) at our institution. Baseline characteristics for all 3 cohorts were similar for age, previous therapies, bone marrow involvement, hematocrit, platelet count, and serum  $\beta_2$ -microglobulin, though serum immunoglobulin M levels were higher in patients treated with CHOP-R ( $P \leq .015$ ). The overall response rates (ORR) and complete response (CR) rates to therapy were as follows: CHOP-R (ORR, 96%; CR, 17%); CVP-R (ORR 88%; CR 12%); CP-R (ORR, 95%; CR, 0%);  $P =$  not significant. Adverse events attributed to therapy showed a higher incidence for neutropenic fever and treatment-related neuropathy for CHOP-R and CVP-R versus CPR ( $P < .03$ ). The results of this study demonstrate comparable responses among patients with WM receiving CHOP-R, CVP-R, or CP-R, though a significantly higher incidence of treatment-related neuropathy and febrile neutropenia was observed among patients treated with CVP-R and CHOP-R versus CP-R. The use of CP-R might provide analogous treatment responses to more intense cyclophosphamide-based regimens while minimizing treatment-related complications in patients with WM.

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## Introduction

Waldenström's macroglobulinemia (WM) is an indolent B-cell non-Hodgkin lymphoma (NHL) characterized by bone marrow (BM) infiltration with lymphoplasmacytic cells and an immunoglobulin (Ig) M monoclonal gammopathy.<sup>1,2</sup> The use of cyclophosphamide-based therapy has been an important treatment option for patients with indolent NHL, including WM,<sup>3</sup> though the optimal cyclophosphamide combination regimen remains to be clarified.

Since its approval in 1997, the monoclonal antibody rituximab has been widely adopted both alone and as a component of combination therapy for the treatment of patients with indolent NHL, including WM. In several randomized studies,

the inclusion of rituximab in cyclophosphamide-based regimens such as CVP (cyclophosphamide/vincristine/prednisone) and CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) led to higher overall and complete response rates as well as improvements in progression-free and/or overall survival in patients with indolent NHL.<sup>4,5</sup> Similar benefits were also demonstrated in a study by the German Low Grade Study Group in patients with WM who received CHOP-R (CHOP plus rituximab) versus CHOP.<sup>6</sup>

Although the above studies have supported the inclusion of rituximab to cyclophosphamide-based therapy, the ideal regimen and the value of including doxorubicin and vincristine with cyclophosphamide-based therapy remains to be clarified. Dimopoulos et al recently reported that the combination of DRC (dexamethasone/rituximab/cyclophosphamide) led to overall and complete responses in 83% and 7% of the patients with WM and a 2-year progression-free survival (PFS) rate of 67%,<sup>7</sup> which appear on par with those results achieved in a comparable population of patients with untreated WM who received CHOP-R.<sup>6</sup> As such, we undertook this study comparing the activity and toxicity associated with CHOP-R, CVP-R, and CP-R in patients with WM followed at our institution.

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## Patients and Methods

### Patients

We identified symptomatic patients with the clinicopathologic diagnosis of WM<sup>8</sup> who received treatment with CHOP-R, CVP-R, or CP-R at our institution from January 1, 2000, to August 1, 2008. The endpoints for this study were comparison of the overall, major, and complete response rates; PFS; improvements in hematologic function; treatment-related adverse events, including occurrence of febrile neutropenia, hospitalizations, neuropathy, and occurrence of the rituximab-related “IgM flare”; and need for interventional plasmapheresis as a result of the “IgM flare.”<sup>8-10</sup>

### Response Assessment

Response determinations were made using modified consensus panel criteria from the Third International Workshop on WM<sup>11</sup> and response rates (RRs) determined on an intent-to-treat basis. A complete response (CR) was defined as having resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. A near-CR (nCR) was defined as fulfilling all CR criteria in the presence of positive immunofixation study. Patients with very good partial responses (VGPRs), partial responses (PRs), and minor responses (MRs) were defined as  $\geq 90\%$ , 50%-89%, and 25%-49% reduction in serum IgM levels, respectively. Progressive disease occurred when  $> 25\%$  increase in serum IgM level or progression of clinically significant disease parameters was observed. Time to disease progression (TTP) was calculated from the start of therapy using the Kaplan-Meier method.

### Therapy

Therapy with CHOP-R consisted of intravenous (I.V.) cyclophosphamide (750 mg/m<sup>2</sup>), doxorubicin (50 mg/m<sup>2</sup>), vincristine (1.4 mg/m<sup>2</sup>; maximum 2 mg), and rituximab (375 mg/m<sup>2</sup>) delivered on day 1, along with prednisone administered orally at 100 mg a day on days 1-5. Therapy with CVP-R consisted of I.V. cyclophosphamide (750-1000 mg/m<sup>2</sup>), vincristine (1.4 mg/m<sup>2</sup>; maximum 2 mg), and rituximab (375 mg/m<sup>2</sup>) delivered on day 1, along with prednisone administered orally at 100 mg/day on days 1-5. Therapy with CP-R consisted of I.V. cyclophosphamide (1000 mg/m<sup>2</sup>), and rituximab (375 mg/m<sup>2</sup>) delivered on day 1, along with prednisone administered orally at 100 mg/day on days 1-5. Growth factors (granulocyte colony-stimulating factor, erythropoietin) were used in accordance with the American Society of Clinical Oncology guidelines and at the treating physician's discretion.

### Statistical Analysis

Comparison of pre- and post-treatment parameters was performed using a 2-tailed Student *t* test on Microsoft Excel software. For all nonparametric testing of pre- and posttreatment responses, 2-tailed Fisher exact test (VassarStats) was used. Analysis of TTP was performed using the log-rank test. If progression was not observed for a given patient, data were censored at the last available observation. A *P* value  $\leq .05$  was deemed to be significant for the above studies.

**Table 1** Baseline Characteristics for Patients with Waldenström's Macroglobulinemia Treated with CHOP-R, CVP-R, or CP-R

| Characteristic                        | CHOP-R<br>(n = 23)   | CVP-R<br>(n = 16)   | CP-R<br>(n = 19)    |
|---------------------------------------|----------------------|---------------------|---------------------|
| Median Age, Years (Range)             | 54 (42-74)           | 60 (32-81)          | 65 (42-74)          |
| Median Previous Therapies, n (Range)  | 0 (0-2)              | 1 (0-3)             | 0 (0-2)             |
| No Previous Therapy, %                | 57                   | 29                  | 63                  |
| Median BM Involvement, % (Range)      | 50 (5-90)            | 50 (20-90)          | 45 (5-95)           |
| Serum IgM, mg/dL (Range)              | 5190<br>(612-12,400) | 2515<br>(566-7180)* | 2665<br>(551-6750)* |
| Hematocrit, %                         | 31.3                 | 30.2                | 33.4                |
| Platelet Count, $\times 10^9/L$       | 242                  | 169                 | 270                 |
| $\beta_2$ -Microglobulin, mg/L        | 3.6                  | 3.3                 | 2.4                 |
| Adenopathy and/or Splenomegaly, n (%) | 8 (34.7)             | 4 (25)              | 6 (31.6)            |
| Cycles of Therapy, n (Range)          | 6 (3-6)              | 6 (3-8)             | 6 (4-8)             |

*P* values were nonsignificant for all cohort comparisons except as noted in Table 1.

\**P* = .015 and *P* = .014 for serum IgM level comparisons to CHOP-R cohort.

Abbreviations: BM = bone marrow; CHOP-R = cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab; CP-R = cyclophosphamide/prednisone plus rituximab; CVP-R = cyclophosphamide/vincristine/prednisone plus rituximab; Ig = immunoglobulin

## Results

### Baseline Characteristics

The baseline characteristics for patients treated with CHOP-R, CVP-R, or CP-R are shown in Table 1. We identified 23 patients who were treated with CHOP-R. These patients had a median age of 54 years (range, 42-74 years) and a median of 0 previous therapies (range, 0-2 therapies). A total of 13 patients (57%) had no previous treatment. The median BM involvement with lymphoplasmacytic cells was 50% (range, 5%-90%); 8 patients (34.7%) had adenopathy and/or splenomegaly, and the median serum IgM was 5190 mg/dL (range, 612-12,400 mg/dL). The median pre-therapy hematocrit and platelet counts for these patients were 31% (range, 22%-45%) and 239,000 (range, 69,000-423,000 cells/ $\mu$ L), respectively. Moreover, the median pre-therapy serum  $\beta_2$ -microglobulin ( $\beta_2$ M) for these patients was 3.6 mg/L (range, 1.3-8.8 mg/L). The median number of cycles of CHOP-R received was 6 (range, 3-6 cycles).

We identified 16 patients treated with CVP-R. These patients had a median age of 60 years (range, 32-81 years) and had a median of 1 previous therapy (range, 0-3 therapies). A total of 5 patients (29%) had no previous treatment. Median BM involvement with lymphoplasmacytic cells was 50% (range, 20%-90%); 4 patients (25%) had adenopathy and/or splenomegaly, and the median serum IgM was 2515 mg/dL (range, 566-7180 mg/dL). Median pre-therapy hematocrit and platelet counts for the patients in the CVP-R group were 30% (range, 21%-38%) and 181,000 (range, 65,000-463,000 cells/ $\mu$ L), respectively. Moreover, the median pre-therapy  $\beta_2$ M for these patients was 2.7 g/L (range, 1.6-7 g/L). The median number of cycles of CVP-R received was 6 (range, 3-8 cycles).

**Table 2** Response Assessments for Patients with Waldenström's Macroglobulinemia Treated with CHOP-R, CVP-R, or CP-R

| Response Assessments                     | CHOP-R (n = 23) | CVP-R (n = 16) | CP-R (n = 19) |
|--|-----------------|----------------|---------------|
| Overall Responders, n (%)                | 22 (96)         | 14 (88)        | 18 (95)       |
| Partial Responders, n (%)                | 10 (44)         | 7 (44)         | 14 (74)       |
| Very Good Partial Responders, n (%)      | 2 (8.7)         | 1 (6.3)        | 0             |
| Complete/Near-Complete Responders, n (%) | 4 (17)          | 2 (12)         | 0             |
| Median Change in sIgM, %                 | -83.2           | -65.5          | -56.2         |
| Improvement in Hematocrit, n (> 2%)      | 19 (83%)        | 11 (68%)       | 12 (63%)      |
| Time to Progression, Months              | 18              | > 35           | > 20          |

P values were nonsignificant for all cohort comparisons.

Abbreviations: CHOP-R = cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab; CP-R = cyclophosphamide/prednisone plus rituximab; CVP-R = cyclophosphamide/vincristine/prednisone plus rituximab; sIgM = serum immunoglobulin

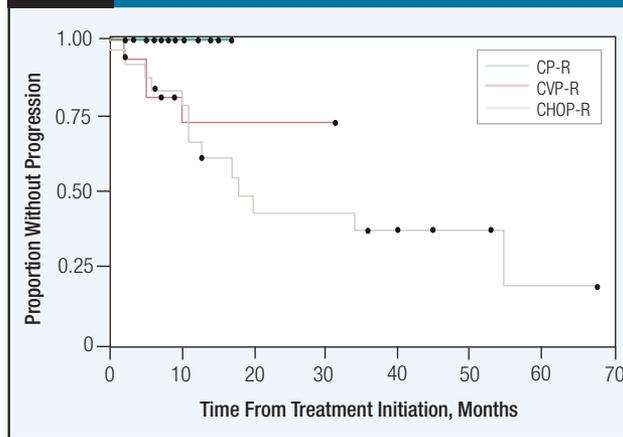
Lastly, we identified 19 patients who were treated with CP-R. These patients had a median age of 65 years (range, 42-74 years) and a median of 0 previous therapies (range, 0-2 therapies). A total of 12 patients (63%) had no previous treatment. Median BM involvement with lymphoplasmacytic cells was 45% (range, 5%-95%); 6 patients (31.6%) had adenopathy and/or splenomegaly, and the median serum IgM level was 2665 mg/dL (range, 551-6750 mg/dL). Median pre-therapy hematocrit and platelet counts for these patients were 33% (range, 27%-49%) and 271,000 (range, 42,000-444,000 cells/ $\mu$ L), respectively. Moreover, the median pre-therapy  $\beta$ 2M was 2.4 g/L (range, 1.3-7.7 g/L). The median number of cycles of CP-R received was 6 (range, 4-8 cycles).

Comparison of baseline characteristics for all 3 cohorts (Table 1) revealed no significant differences except for serum IgM levels between patients treated with CHOP-R versus CVP-R ( $P = .015$ ) and between patients treated with CHOP-R versus CP-R ( $P = .014$ ).

**Response to Treatment**

The response assessments for the 3 cohorts are summarized in Table 2. Among patients who received CHOP-R, median IgM levels declined from 5190 mg/dL (range, 612-12,400 mg/dL) to 875 mg/dL (range, 55-6450 mg/dL) at best response ( $P \leq .001$ ). Before treatment, 16 of 23 patients (70%) exhibited an IgM level  $\geq 3000$  mg/dL; following treatment, only 6 of 23 patients (26%) had an IgM level  $\geq 3000$  mg/dL ( $P = .007$ ). A significant increase in the median hematocrit was noted for all patients from 31.3% (range, 22.3%-44.6%) before therapy to 38.3% (range, 21%-44.7%) following treatment ( $P = .002$ ), with 19 of the 23 patients (83%) demonstrating an absolute rise in hematocrit of  $> 2\%$ . Before therapy, the median platelet count was  $242 \times 10^9/L$  (range,  $69-423 \times 10^9/L$ ); following treatment, the median platelet count was  $221 \times 10^9/L$  (range,  $7-359 \times 10^9/L$ );  $P = .29$ . Before therapy, 10 (43.4%) and 2 (8.6%) of the 23 patients demonstrated a hematocrit  $\leq 30\%$  and a platelet count of  $\leq 100 \times 10^9/L$ , respectively. Following therapy, 2 (8.6%) and 2 (8.6%) of

**Figure 1** Baseline Characteristics for Patients with WM Treated with CHOP-R CVP-R, or CP-R



$\chi^2$  (degree of freedom = 2) = 6.075;  $P = .048$  for difference among the 3 treatment groups by log-rank analysis.

Abbreviations: CHOP-R = cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab; CP-R = cyclophosphamide/prednisone plus rituximab; CVP-R = cyclophosphamide/vincristine/prednisone plus rituximab; WM = Waldenström's macroglobulinemia

the 23 patients demonstrated a hematocrit of  $\leq 30\%$  and platelet count of  $\leq 100 \times 10^9/L$  ( $P = .016$  and  $.99$ , respectively). Of 23 patients, 22 had at least an MR after CHOP-R therapy, for an overall RR (ORR) of 96%, which included 4 CRs/nCRs (17%), 2 VGPRs (8.7%), 10 PRs (44%), and 6 MRs (26%), respectively. With a median follow-up of 25 months (range, 6-69.1 months), all patients in this cohort are alive, and 10 patients remain free of disease progression. The median TTP for these patients was 18 months (Figure 1).

Among patients who received CVP-R, median IgM levels declined from 2515 mg/dL (range, 566-7180 mg/dL) to 869 mg/dL (range, 48-4460 mg/dL) at best response ( $P \leq .001$ ). Before treatment, 6 of 16 patients (38%) exhibited an IgM level  $\geq 3000$  mg/dL; after treatment, 2 of 16 patients (12.5%) had an IgM level  $\geq 3000$  mg/dL ( $P = .22$ ). A significant increase in the median hematocrit was noted for all patients from 30.2% (range, 21.3%-37.5%) before therapy to 34.8% (range, 26.1%-43%) after treatment ( $P = .005$ ), with 11 of the 16 patients (68%) demonstrating an absolute rise in hematocrit of  $> 2\%$ . Before therapy, the median platelet count was  $181 \times 10^9/L$  (range,  $65-463 \times 10^9/L$ ); after treatment, the median platelet count was  $217 \times 10^9/L$  (range,  $101-390 \times 10^9/L$ );  $P = .49$ . Before therapy, 8 (50%) and 1 (6.3%) of the 16 patients demonstrated a hematocrit  $\leq 30\%$  and a platelet count of  $\leq 100 \times 10^9/L$ , respectively. After therapy, 2 (12.5%) and none of the 16 patients demonstrated a hematocrit of  $\leq 30\%$  and platelet count of  $\leq 100 \times 10^9/L$  ( $P = .05$  and  $.99$ , respectively). Of 16 patients, 14 had at least an MR following CVP-R therapy, for an ORR of 88%, which included 2 CRs/nCRs (12%), 1 VGPR (6.3%), 7 PRs (44%), and 4 MRs (25%), respectively. With a median follow-up of 15 months (range, 3-28.7+ months), all patients in this cohort are alive, and 12 patients remain free of disease progression. Estimation for median TTP was not possible because of insufficient events but exceeds 35 months (Figure 1).

Among patients who received CP-R, median IgM levels declined from 2620 mg/dL (range, 551-6750 mg/dL) to 1150 mg/dL (range,

167-4770 mg/dL) at best response ( $P \leq .001$ ). Before treatment, 7 of 19 patients (37%) exhibited an IgM level  $\geq 3000$  mg/dL; after treatment, 1 of 19 patients (5.2%) had an IgM level  $\geq 3000$  mg/dL ( $P = .04$ ). A significant increase in the median hematocrit was noted for all patients from 33.4% (range, 27.1%-48.5%) before therapy to 38.3% (range, 30.4%-42.6%) following treatment ( $P = .1$ ), with 12 of the 19 patients (63%) demonstrating an absolute rise in hematocrit of  $> 2\%$ . Before therapy, the median platelet count was  $270 \times 10^9/L$  (range,  $42-444 \times 10^9/L$ ); after treatment, the median platelet count was  $208 \times 10^9/L$  (range,  $137-343 \times 10^9/L$ );  $P = .56$ . Before therapy, 4 (21.1%) and 3 (15.8%) of the 19 patients demonstrated a hematocrit  $\leq 30\%$  and a platelet count of  $\leq 100 \times 10^9/L$ , respectively. Following therapy, none of the 19 patients demonstrated a hematocrit of  $\leq 30\%$  and platelet count of  $\leq 100 \times 10^9/L$  ( $P = .1$  and  $P = .23$ , respectively). Of 19 patients, 18 had at least an MR following CP-R therapy, for an ORR of 95%, with 14 of the patients (74%) having a major response. No CRs, nCRs, or VGPRs were observed. With a median follow-up of 9 months (range, 2.86-17.9+ months), all patients are alive and free of disease progression. Estimation for median TTP was not possible because of insufficient events but exceeds 20 months (Figure 1).

Comparison of all response parameters, including categorical response rates (overall, major [PR or better], and CR rates), median serum IgM reduction, and percentage of patients demonstrating at least an absolute 2% increase in hematocrit revealed no significant differences, although a trend for greater serum IgM reductions and more CRs/nCRs was observed with CHOP-R and CVP-R versus CP-R. By log-rank analysis, TTP was found to be statistically significant among the 3 treatment groups ( $\chi^2$  [degree of freedom = 2] = 6.075;  $P = .048$ ), with longer TTPs estimated for patients treated with CP-R and CVP-R versus CHOP-R.

### Toxicities

We next analyzed treatment related adverse events. Treatment-related neuropathy, febrile neutropenia, and hemorrhagic cystitis were among the most commonly encountered toxicities ( $> 5\%$ ). We also evaluated treatment related hospitalizations, occurrence of a rituximab-related IgM flare, and need for plasmapheresis among the 3 treatment cohorts. The most common treatment-related toxicity was neuropathy (any grade), which occurred in 11 (47.8%), 11 (68.8%), and none of the patients who received CHOP-R, CVP-R, and CP-R, respectively, and was attributable to vincristine ( $P < .001$  for CHOP-R or CVP-R versus CP-R). Febrile neutropenia (any grade) occurred in 4 (17%), 2 (12%), and none of the patients who received CHOP-R, CVP-R, CP-R, respectively ( $P =$  not significant [NS]). Treatment-related hemorrhagic cystitis occurred in 2 patients (8.6%) treated with CHOP-R but in none of the patients treated with CVP-R or CP-R. Among patients who received CHOP-R, CVP-R, CP-R, treatment-related hospitalizations occurred in 4 (17%), 4 (25%), and none of the patients, respectively ( $P =$  NS).

### Rituximab-Related "IgM Flare"

We also analyzed the occurrence of the rituximab related "IgM flare" and necessity for interventional plasmapheresis because of the IgM flare in an attempt to discern if doxorubicin- and vincristine-inclusive cyclophosphamide-based therapies could attenuate the

flare phenomenon previously reported by us and others in patients WM receiving rituximab alone.<sup>8-10</sup> Among the 23 patients who received CHOP-R, 6 (27.3%) experienced an IgM flare, and 3 (13.6%) required plasmapheresis for the IgM flare. For patients treated with CVP-R, 4 of 16 (25%) experienced an IgM flare, and 2 (12.5%) required plasmapheresis for the flare. Of the 19 patients who received CP-R, 5 (26.3%) had an IgM flare, and 3 (15.8%) required plasmapheresis. Comparison of the incidence of IgM flare and interventional plasmapheresis for the IgM flare among the 3 treatment cohorts revealed no significant differences.

## Discussion

Since the adoption of rituximab, the importance of doxorubicin and vincristine as treatment components remains to be clarified in indolent NHL, including WM. To our knowledge, no randomized clinical trials have been conducted in any indolent NHL in order to clarify this important point because the use of doxorubicin and vincristine are associated with many serious adverse events, including alopecia, myelosuppression, and cardiac toxicity for the former and peripheral neuropathy for the latter. As such, we performed this retrospective study in order to evaluate outcomes in patients with WM who received treatment with CHOP-R, CVP-R, and CP-R.

The results of this study demonstrated comparable overall and major (PR or better) RRs among patients who received CHOP-R, CVP-R, and CP-R. However, a trend toward more CRs/nCRs was observed in patients who received CHOP-R and CVP-R in comparison to CP-R, which will need to be validated in larger comparative studies. The value of attaining VGPRs or better, ie,  $\geq 90\%$  reduction in serum IgM, has been raised in a recent study by us in patients treated with fludarabine and rituximab, wherein a longer median TTP was noted in patients attaining at least a VGPR.<sup>12</sup> Longer-term follow-up will be required to validate the Kaplan-Meier estimates available at this time, particularly for patients who received CVP-R and CP-R in this series.

Another consideration in this study was the greater number of patients with elevated serum IgM levels in the CHOP-R cohort. In some, but not all studies, higher serum IgM levels were correlated with inferior prognosis.<sup>13-15</sup> Higher serum IgM levels have also been associated with inferior responses to rituximab in 2 studies.<sup>8,16</sup> Indeed, the major (ie,  $\geq 50\%$  reduction in disease) and CR rates for patients with serum IgM  $\geq 5000$  mg/dL treated with CHOP-R in this series were 50% (6 of 12 patients) and 0%; by comparison, the major and CR rates in patients with pre-therapy serum IgM levels of  $< 5000$  mg/dL were 91% (10 of 11 patients) and 36% (4 of 11 patients;  $P = .06$  and  $P = .09$ , respectively). Time to progression was also shorter among patients with pre-therapy serum IgM levels  $> 5000$  mg/dL (11.1 months) versus  $< 5000$  mg/dL (17.8 months;  $P = .42$ ). No significant difference in bone marrow involvement for these 2 patients cohorts was observed ( $P = .95$ ). A similar comparison for patients treated with CVP-R and CP-R could not be undertaken because considerably fewer patients treated with CVP-R ( $n = 3$ ) and CP-R ( $n = 1$ ) had serum IgM levels  $\geq 5000$  mg/dL.

Despite these considerations, the outcomes in this study are comparable to results obtained by others examining doxorubicin- and vincristine-sparing cyclophosphamide-based rituximab combination therapy. Buske et al reported ORRs and CR rates of 91% and 11% in patients with WM receiving first-line CHOP-R,<sup>6</sup> which are analogous

to those rates observed in our series. In a comparable population of patients with WM, Dimopoulos et al reported ORRs and CR rates of 83% and 7% with rituximab/cyclophosphamide/dexamethasone (RCD),<sup>7</sup> a regimen similar to CP-R that uses oral (1 gm/m<sup>2</sup> over 5 days) instead of intravenous (I.V.; 1 gm/m<sup>2</sup> on day 1) cyclophosphamide and a more attenuated course of steroids, ie, dexamethasone 20 mg I.V. on day 1 of RCD versus prednisone 100 mg orally a day for 5 days in CP-R. The outcomes of RCD are comparable with those we observed in patients receiving CP-R but are also comparable with those reported with CHOP-R in the study reported by Buske et al.<sup>6</sup>

Although the results of this study suggest analogous overall responses in patients with WM receiving CHOP-R, CVP-R, and CP-R, certain adverse events were more pronounced in patients receiving treatment with CHOP-R or CVP-R versus CP-R. Neuropathy was significantly more pronounced in patients who received vincristine-containing CHOP-R and CVP-R versus CP-R and, in some patients, was quite debilitating. We have reported an exaggeration of treatment-related neuropathy with other neuropathic agents such as thalidomide and bortezomib in patients with WM, in whom there appears to be an increased tendency to develop treatment-related neuropathy compared with patients with other B-cell disorders.<sup>17,18</sup> In addition to the development of neuropathy, a trend toward an increased incidence of febrile neutropenia and hospitalizations was observed in patients treated with CHOP-R > CVP-R > CP-R. Lastly, the addition of doxorubicin and/or vincristine to cyclophosphamide-based rituximab therapy did not obviate development of the rituximab-induced IgM flare and interventional plasmapheresis, which occurred in approximately 25% and 15% of patients treated on any of the 3 regimens, respectively. As such, close monitoring of serum IgM levels and empiric plasmapheresis for patients with WM displaying high serum IgM levels or viscosity levels (ie, > 5000 mg/dL or 3.5 cP, respectively) should be considered in patients treated with CHOP-R, CVP-R, or CP-R.<sup>9,17,18</sup>

## Conclusion

The results of this study suggest that in WM, the use of doxorubicin- and vincristine-sparing cyclophosphamide-based rituximab regimens such as CP-R might provide analogous treatment responses to more intense cyclophosphamide-based regimens while minimizing treatment-related complications.

## References

- Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström Macroglobulinemia. *Semin Oncol* 2003; 30:110-5.
- Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; 17:3835-49.
- Dimopoulos MA, Gertz MA, Kastritis E, et al. Update on treatment recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia. *J Clin Oncol* 2009; 27:120-6.
- Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol* 2008; 26:4579-86.
- Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005; 106:3725-32.
- Buske C, Hoster E, Dreyling M, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). *Leukemia* 2009; 23:153-61.
- Dimopoulos MA, Anagnostopoulos A, Kyrtonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol* 2007; 25:3344-9.
- Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab. *J Clin Oncol* 2002; 20:2327-33.
- Treon SP, Branagan AR, Hunter Z, et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenström's macroglobulinemia. *Ann Oncol* 2004; 15:1481-3.
- Ghobrial IM, Fonseca R, Greipp PR, et al. Initial immunoglobulin M 'flare' after rituximab therapy in patients with Waldenström Macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer* 2004; 101:2593-8.
- Kimby E, Treon SP, Anagnostopoulos A, et al. Update on recommendations for assessing response from the Third International Workshop on Waldenström's Macroglobulinemia. *Clin Lymphoma Myeloma* 2006; 6:380-3.
- Treon SP, Branagan AR, Ioakimidis L, et al. Long term outcomes to fludarabine and rituximab in Waldenström's macroglobulinemia. *Blood* 2008; Epub ahead of print.
- Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system (IPSS) for Waldenström's macroglobulinemia. *Blood* 2009; [In press].
- Morel P, Monconduit M, Jacomy D, et al. Prognostic factors in Waldenström macroglobulinemia: a report on 232 patients with the description of a new scoring system and its validation on 253 other patients. *Blood* 2000; 96:852-8.
- Dhodapkar MV, Jacobson JL, Gertz MA, et al. Prognostic factors and response to fludarabine therapy in patients with Waldenström macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood* 2001; 98:41-8.
- Treon SP, Emmanouilides C, Kimby E, et al. Extended rituximab therapy in Waldenström's macroglobulinemia. *Ann Oncol* 2005; 16:132-8.
- Treon SP, Soumerai JD, Branagan AR, et al. Thalidomide and rituximab in Waldenström macroglobulinemia. *Blood* 2008; 112:4452-7.
- Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenström's Macroglobulinemia with bortezomib, dexamethasone and rituximab: results of WMCTG Clinical Trial 05-180. *J Clin Oncol* 2009. In press.