# Cyclophosphamide, bortezomib and dexamethasone (CyBorD) combination in Waldenstrom Macroglobulinemia

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**To the Editor:**

Waldenstrom Macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma with many patients showing progressive disease despite the recent advances of novel therapeutic agents year(1-3). The combination of bortezomib, dexamethasone, and cyclophosphamide (CyBorD) has been studied in Multiple Myeloma showing overall response rate of 88%, and being used as one of the standard of care options for this plasma cell dyscrasia(4-6). Here we report a retrospective report of patients treated at one academic center with the combination ofCyBorD with or without rituximab in patients with WM.

A retrospective analysis was performed on a database of patients diagnosed with WM and seen at the Dana-Farber Cancer Institute (DFCI) in Boston, Massachusetts. Approval for this protocol was obtained from DFCI and was in accordance with the Declaration of Helsinki. Medical files were reviewed for patients who had been treated with CyBorD between 01/2010 and 01/2014. Fifteen patients were identified as being treated with this combination regimen. Cyclophosphamide was given with different regimens and schedules including 500-1000mg/m2 on day 1 only or 500mg/m2 on days 1 and 8 of a 21 day cycle in 11/15 (73%) patients, while 3 (20%) patients received it at 300mg/m2 on days 1, 8, and 15 of a 28 day cycle. Bortezomib was given at standard dosing of 1.3mg/m2 on a twice-weekly regimen in 9/15 (60%), while 6 patients (40%) received weekly bortezomib on days 1, 8 and 15 to avoid neuropathy. Seven patients (47%) also received rituximab in addition to the CyBorD regimen.

The patients' baseline characteristics are shown in Table 1. Overall response rate (ORR, defined as at least MR) was observed in 14/15 (93%, CI: 70-99%), and the major response rate (defined as at least PR) was observed in 8 patients (53%, CI: 30-75%). One patient (7%, CI 1-30%) achieved complete response (CR), 7 patients (47%, CI 25-70%) achieved partial response (PR), and 6 patients (40%, CI 20-64%) achieved minor response (MR). Cryoglobulinemia resolved in 3 of 4 (75%) patients who had positive cryoglobulinemia. Only 1 (6%) patient showed progressive disease after 3 cycles of therapy. The responses in the 4 patients who were previously untreated were 1 CR, 1

PR and 2 MR for 100% ORR. The median time to best response was 2 months (range, 1-8 months). The median proportion of bone marrow involvement with LPL at the time of initiation of therapy was 80% (range, 40-90%). The median proportion at the end of therapy was 10% (range, 0-90%). The median TTP for the entire cohort was 9.7 months (range, 1-44 months; Figure 1). The median time to progression for the 4 patients who were previously untreated was 18.6 months (range, 5-37 months). The median DOR for responders was 7.3 months (range, 1-43 months; Figure 2). Grade 3-4 toxicities that required dose modifications/delays or interruptions included neuropathy (26%), cytopenias (20%), bacteremia (7%), rituximab reactions (7%) and atrial fibrillation (7%). One patient (7%) discontinued therapy due to toxicity with a G3 E. coli bacteremia after cycle 1 of therapy.

This data demonstrate that this regimen is highly effective in WM even in patients who cannot tolerate or cannot receive rituximab. New therapeutic options such as Ibrutinib or everolimus maybe used more frequently in patients with WM in the near future. However, these agents do not always induce a significant bone marrow response in comparison to the IgM response observed in the serum (7, 8). However, the significant bone marrow response in many patients with CyBorD can make it an attractive option for achieving complete remissions in patients who do not achieve adequate bone marrow responses with other agents. In addition, in the era of highly expensive combinations of chemotherapeutic agents, the combination of CyBorD may provide a less expensive and highly effective alternative that can be used more broadly in many developing countries with high responses.

As with other retrospective studies, ours has many limitations including a small number of patients, selection bias, and different dosing schemas within this cohort. Despite this, it provides preliminary evidence for a highly effective regimen for WM that should be further validated in larger prospective trials.

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## FIGURE LEGENDS

**Figure 1:** Swimmer's plot for time to progression of all 15 patients. Green color denotes CR, blue denotes PR, orange denotes MR and red denotes PD. X indicates death on follow up. X-axis is months on treatment, y-axis is response.

**Figure 2:** Kaplan-Meier estimates for **(A)** time to progression and **(B)** duration of response in 15 patients with relapsed and refractory Waldenström Macroglobulinemia treated with CyBorD.

**Table 1 Baseline characteristics.**

| Characteristics | No. | % |
|---|---|---|
| Age, years | | |
| Median | 63 | |
| Range | 45-76 | |
| Sex, male | 9 | 60% |
| International scoring system for WM | | |
| Low | 1 | 6 |
| Intermediate | 7 | 47 |
| High | 7 | 47 |
| Baseline IgM prior to CyBorD | | |
| Median | 3,540 | |
| Range | 1530-7700 | |
| Baseline M-spike prior to CyBorD | | |
| Median | 2.06 | |
| Range | 0.07-4.54 | |
| Baseline hemoglobin, g/dL | | |
| Median | 8.7 | |
| Range | 6.7-13.4 | |
| Baseline platelet count, $10^9$/L | | |
| Median | 145 | |
| Range | 30-468 | |
| B2-microglobulin >3mg/dL | 14 | 93 |
| Bone marrow percent involvement* | | |
| Median | 70 | |
| Range | 40-90 | |
| No. of prior therapies | | |
| No prior therapy | 4 | 27 |
| Prior therapy | 11 | 73 |
| Median number of prior therapy | 4 | range (1-8) |
| 1-3 | 4/11 | 36 |
| 4-6 | 5/11 | 45 |
| >6 | 2/11 | 18 |
| Prior therapy (# of patients) | | |
| Rituximab | 11 | 73 |
| Bortezomib | 7 | 47 |
| Alkylators | 5 | 33 |
| Purine nucleoside analogue | 4 | 27 |
| Thalidomide, lenalidomide | 2 | 13 |
| Interferon | 1 | 7 |
| Clinical trial based therapy | | |
| Panobinostat | 4 | 27 |
| Enzastaurin | 2 | 13 |
| Perifosine | 2 | 13 |
| Everolimus | 3 | 20 |
| No. of patients with concurrent rituximab with CyborD | 7 | 47 |

**Table 2: Categorical response**

| | **Patients N=15** |
|---|---|
| **ORR (MR or better)** | 14(93%)<br>(95% CI: 70-99%) |
| **ORR (PR or better)** | 8 (53%)<br>(95% CI: 30-75%) |
| **CR** | 1 (7%)<br>(95% CI: 1-30%) |
| **PR** | 7 (47%)<br>(95% CI: 25-70%) |
| **MR** | 6 (40%)<br>(95% CI:20-64%) |
| **Progressive disease** | 1 (7%)<br>(95% CI:1-30%) |

Figure 1

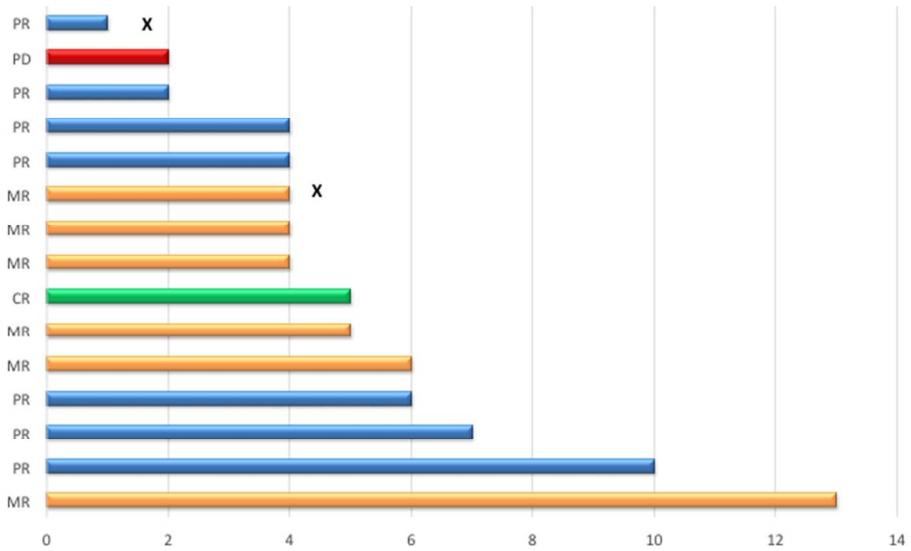


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Figure 2A

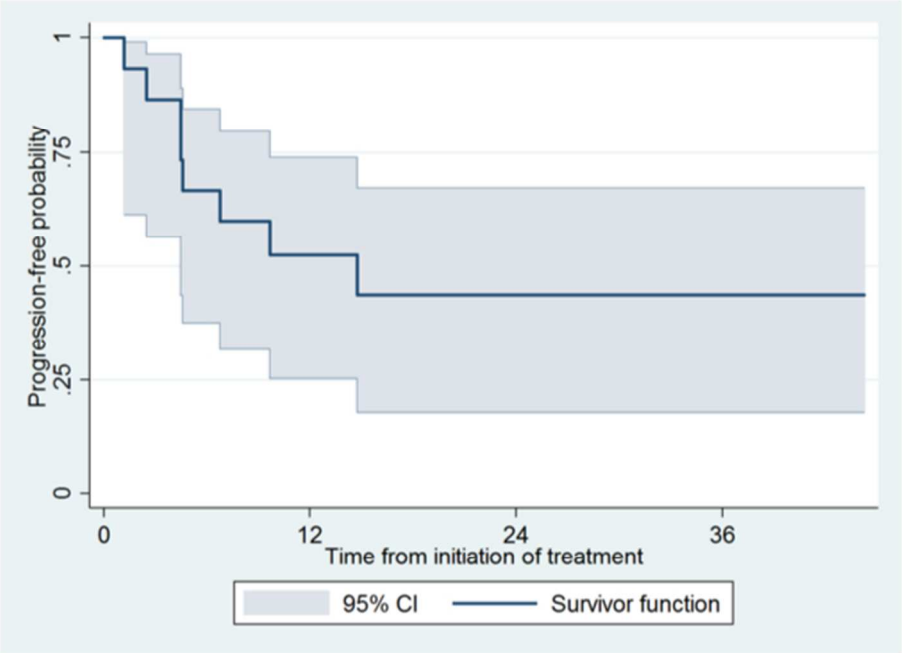


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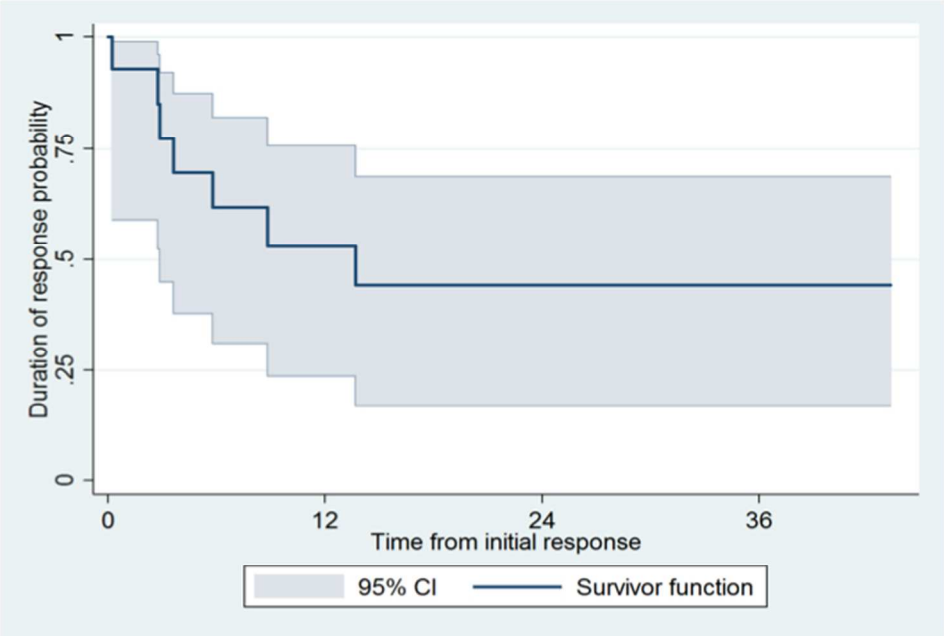
Figure 2B

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