Cyclophosphamide, bortezomib, and dexamethasone combination in Waldenstrom macroglobulinemia

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 [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 of CyBorD with or without rituximab in patients with WM.

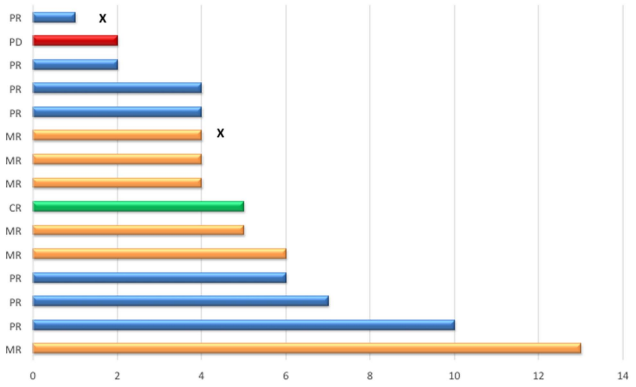

Figure 1. Swimmer's plot for time to progression of all 15 patients. Green color denotes CR, blue denotes PR, orange denotes MR, and red denotes PD. X indicates death on follow-up. *X*-axis is months on treatment, *y*-axis is response. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

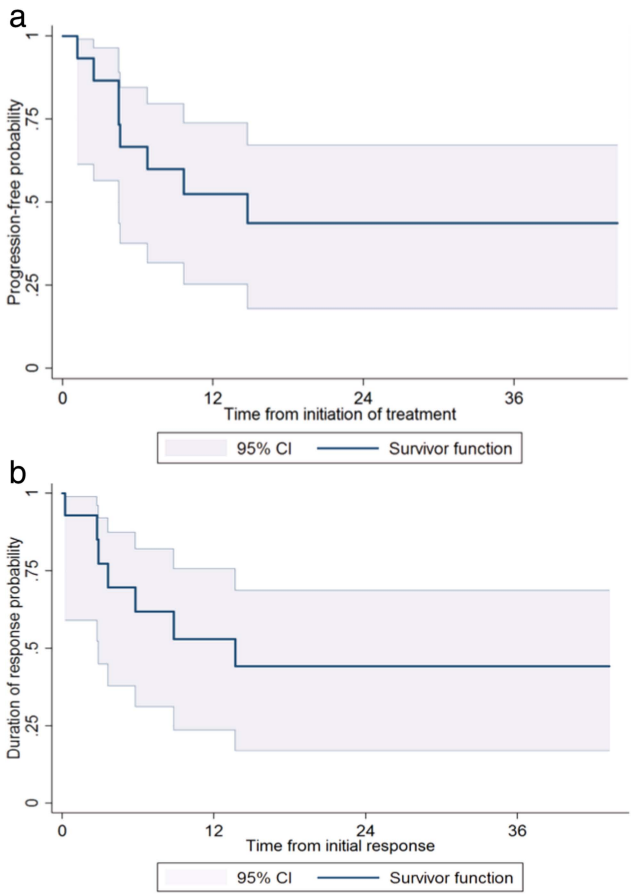

Figure 2. Kaplan–Meier estimates for **(A)** time to progression and **(B)** duration of response in 15 patients with relapsed and refractory Waldenström macroglobulinemia treated with CyBorD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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 January 2010 and January 2014. Fifteen patients were identified as being treated with this combination regimen. Cyclophosphamide was given with different regimens and schedules including 500–1,000 mg/m^2 on day 1 only or 500 mg/m^2 on days 1 and 8 of a 21-day cycle in 11/15 (73%) patients, while 3 (20%) patients received it at 300 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Bortezomib was given at standard dosing of 1.3 mg/m^2 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 I. 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%) (Table II). One patient (7%, CI 1–30%) achieved complete response (CR), seven patients (47%, CI 25–70%) achieved partial response (PR), and six patients (40%, CI 20–64%) achieved minor response (MR). Cryoglobulinemia resolved in three of four (75%) patients who had positive cryoglobulinemia. Only one (6%) patient showed progressive disease after three cycles of therapy. The responses in the four patients who were previously

TABLE I. 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	1,530–7,700	
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 >3 mg/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 (no. 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

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TABLE II. Categorical Response

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

untreated were one CR, one PR, and two 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 lymphomplasmacytic lymphoma (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 time to progression (TTP) for the entire cohort was 9.7 months (range, 1–44 months; Fig. 1). The median time to progression for the four 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; Fig. 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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References

1. Treon SP, Hunter ZR, Castillo JJ, Merlini G. Waldenstrom macroglobulinemia. Hematol Oncol Clin N Am 2014; 28:945–70.
2. Sahin I, Leblebjian H, Treon SP, Ghobrial IM. Waldenstrom macroglobulinemia: From biology to treatment. Expert Rev Hematol 2014;7:157–68.
3. Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment recommendations for patients with waldenstrom macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood 2014;124:1404–1411.
4. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: High response rates in a phase II clinical trial. Leukemia 2009;23:1337–1341.
5. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012;119:4391–4394.
6. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood 2010;115:3416–3417.
7. Ghobrial IM, Gertz M, Laplant B, et al. Phase II trial of the oral mammalian target of rapamycin inhibitor everolimus in relapsed or refractory waldenstrom macroglobulinemia. J Clin Oncol 2010;28:1408–1414.
8. Ghobrial IM, Witzig TE, Gertz M, et al. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory waldenstrom macroglobulinemia. Am J Hematol 2014;89:237–242.

Post-remission intensive treatment after induction chemotherapy is feasible in selected elderly patients with acute myeloid leukemia and age ≥75 years: a retrospective analysis of the Rete Ematologica Lombarda

To the Editor: The prognosis of elderly pts with AML is poor with 2- and 5-year overall survival (OS) rates of approximately 10% and 2%, respectively [1]. In elderly pts, the complete remission (CR) rate after induction is around 50% and the relapse rate is of almost 90%. To prevent relapse, pts in CR should receive some form of postremission treatment [2]. There are no comparative trials defining which postremission treatments benefit older pts. Moreover, allogeneic haematopoietic stem cell transplantation is still offered to a minority of pts over 65 years of age [3]. Recently, published guidelines define age 75 as the upper limit to consider pts fit for intensive chemotherapy (IC) [4]. Anyway, it is becoming evident that age alone is not always appropriate to select pts to receive IC.

TABLE I. Pts Characteristics

34 patients

Gender:		**Age**:	
F: 15		average: 76.6	
M: 19		median: 76 (range 75–80)	
Diagnosis (WHO 2001 or 2008 classification):		**Cytogenetics (26 pts evaluable)**:	
AML with minimal differentiation	2	Normal	16
AML w/o maturation	6	inv(16)/t(16;16)	1
AML with maturation	3	+8	2
Acute myelomonocytic leukemia	2	t(3;3)(q21;q26),-7	1
Acute monoblastic/monocytic leukemia	2	t(3;21)(q26;q22)	1
AML following MDS or with MDS related changes	9	t(1;2)(p36;p13)	1
Therapy-related myeloid neoplasms	3	+8, +21	1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH10	2	+19,+13	1
AML with mutated NPM1	4	del7q	1
Biphenotypic leukemia	1	complex	1
WBC × 10e9/L:		**Molecular (18 pts evaluable)**:	
median 38 (range 1,1–215,2)		NPM1 mut only	8
≥ 100 6		NPM1 mut + FLT3ITD	3
50–99.9 8		FLT3ITD only	1
10–49.9 10		CBF-MYH	1
< 10 10		Negative	5