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Original Research Article

Comparative efficacy of triple combination therapies containing either bortezomib or rituximab in treatment-naïve patients with lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)

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Abstract

Purpose: *To evaluate the comparative efficacy of triple combination therapies of cyclophosphamide/dexamethasone containing either bortezomib or rituximab in treatment-naïve patients diagnosed with lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia, LPL/WM).*
Methods: *Symptomatic, untreated patients with LPL/WM diagnosed in the First Affiliated Hospital of Soochow University were enrolled in this study and divided into two groups (BCD and RCD). Group BCD consisted of 16 patients administered bortezomib/cyclophosphamide/dexamethasone, while group RCD (15 patients) received rituximab/cyclophosphamide/dexamethasone. The efficacy of the two therapies and the Kaplan-Meier survival curve of the groups were evaluated.*
Results: *With regard to overall response rate (ORR) and minimal response rate (MRR), there was no statistically significant difference between the 2 groups (100 vs 86.6 %, p = 0.226, and 81.25 vs 60.0 %, p = 0.252, respectively). The median time to minimal response (MR) in the BCD group was 1.3 months, which was shorter compared with that of RCD group (3.5 months, p = 0.026). Treatment-related toxicities (grade>2) were leukopenia, neutropenia, hypohepatia and pneumonia. With a median study follow-up of 27 months, disease in 18 patients (8 vs 10) progressed while 4 patients died (all in RCD group). The estimated median progression free survival (PFS) was 43 and 35 months in groups BCD and RCD, respectively, but the overall survival (OS) rate in 25 months significantly differed between the 2 groups (100 % vs 66.1 %, p = 0.033).*
Conclusion: *The two regimens are active, produced responses and are safe as primary therapies for patients with LPL/WM. However, the response median time was much shorter in group BCD patients, and thus might have better survival benefits.*

Keywords: *Waldenstrom macroglobulinemia, Bortezomib, Rituximab, Cyclophosphamide, Dexamethasone*

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INTRODUCTION

Waldenstrom macroglobulinemia (WM), also known as a special type of Lymphoplasmacytic lymphoma (LPL) is a rare non-invasive non-Hodgkin lymphoma [1], accounting for 1 ~ 2 % of all hematological malignancies that infiltrate through small lymphocytes or plasmacytoid/plasma cells differentiation in the bone marrow, lymphaden, liver or spleen. Waldenström macroglobulinemia (WM) is characterized by bone marrow infiltration with lymphoplasmacytic cells, along with immunoglobulin M (IgM) monoclonal gammopathy. Some patients with LPL have other types of M-protein (IgA and IgG) or do not have monoclonal protein. Most LPL/WM patients are indolent, but 10 - 15 % of them progress rapidly. Treatment is initiated only for patients with symptomatic LPL/WM.

For patients without symptoms, close observation is recommended. The symptoms of the disease include the presence of cytopenia, neuropathy, hyperviscosity, organomegaly or adenopathy, amyloidosis, cold agglutinin disease cryoglobulinemia, and B symptoms. At present, alkylating agents, nucleoside analogues, Rituximab single or combined with alkylator regimen; bortezomib single or its based therapy and Bruton's tyrosine kinase (BTK) inhibitors are available for the treatment of LPL/WM. Agents that limit future treatment options of autologous stem cell transplant (SCT) should be avoided during initial treatment, such as exposure to continuous oral alkylator therapy or nucleoside analogs. Due to the limited availability of medicine in China and because BTKi was not initially approved for these patients, a single agent of anti-CD20 monoclonal antibody, or combined with chemotherapy was as an important standard treatment for a majority patients with LPL/WM.

Bortezomib-based regimens are commonly used treatment approaches in routine practice in patients with high IgM levels, cryoglobulinemia, symptomatic hyperviscosity, or amyloidosis, cold agglutinemia, and renal impairment, or in young patients in whomalkylator or nucleoside analog treatment should be avoided. Both of them are important and effective. Due to the rarity of WM, treatments have been adopted from data derived from phase 2 studies, and rarely from randomized studies that included only patients with other indolent B-cell malignancies or WM. However, the most suitable treatment is still unknown. Therefore, the aim of this study was to undertake a comparative evaluation of the efficacy of therapies that combine cyclophosphamide and dexamethasone with either bortezomib (BCD) or rituximab (RCD) in treatment-naïve patients with LPL/WM.

METHODS

Patients

A total of 31 treatment-naïve patients meeting International Workshop for Waldenstrom macroglobulinemia-2 criteria were enrolled. Immunophenotypic studies by flow cytometry and/or immunohistochemistry were used to support the bone marrow infiltration, with the following immunophenotypic profile: sIgM+, CD19+, CD20+, CD22+ CD5-, CD10-, and CD23; and the demonstrated IgM monoclonal protein in the serum by serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE) as criteria for treatment.

Ethical matters

Enrollment began on July 1, 2015, and closed January 15, 2020. All procedures were performed in studies involving human participants. The study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (approval no. 2016034, NCT02971982), and was carried out according to the guidelines of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [2]. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Final patient evaluations and survival updates were done on June 1, 2020. Serum IgM measurement, Beta-2 microglobulin and complete blood cell counts were done for WM International Prognostic Scoring System (IPSS) which include five adverse covariates [3]: age >65 years, hemoglobulin <115 g/L, platelet count $<100\times10^9$/L, β2-MG >3 mg/l, IgM >70 g/l. Patients presenting with no or 1 of the adverse characteristics and advanced age were classified as low-risk ,patients with 2 adverse characteristics or only advanced age as intermediate-risk, and patients with more than 2 adverse characteristics as high-risk. MYD88 (L265P) gene mutation of bone marrow aspirate was also tested in all the patients.

Treatments

Sixteen patients (Group A) were administered BCD therapy (bortezomib subcutaneous injection 1.3 mg/m^2 on days 1, 4, 8 and 11;

cyclophosphamide intravenous injection 750 mg/m^2 on day 1; and dexamethasone 20 mg oral administration on days 1, 2, 4, 5, 8, 9, 11 and 12). Another 15 patients (Group B) were administered RCD (rituximab 375mg/m^2 intravenous injection on days 1, 4, 8 and 11; cyclophosphamide 750 mg/m^2 intravenous injection on day 1; and dexamethasone 20 mg oral administration on day 1, 2, 4, 5, 8, 9, 11 and 12). Thirteen patients in BCD group completed 6 cycles of therapy while 12 patients among them received another 2 cycles of BD regimen as maintenance therapy. One of the remaining 3 patients received 5 cycles, one received 4 cycles and discontinued because of repeated pulmonary infection, and the last patient received 3 cycles, but self-withheld therapy for personal reasons. Eleven patients in RCD group completed 6 cycles of therapy, but 6 of the patients among them received another 2 cycles of R single regimen as maintenance therapy. Six patients received 5 cycles of therapy and one patient received only one cycle of RCD, followed by a palliative treatment, and his condition progressed 20 months later during the follow-up.

The primary end point of the study was the determination of ORR, which included minor responses and MRR, consisting of partial response (PR), VGPR and complete response (CR) according to International Workshop for Waldenstrom Macroglobulinimia-6 criteria between the two groups [4, 5].

Data analysis

Pairwise comparisons were made using Wilcoxon singed-rank test. Progression-free survival (PFS) was defined as time between the initiation of therapy and the date of progression, death, or last follow-up. Overall survival (OS) was defined as the time between the initiation of therapy and the date of death (whatever the cause). For time-to–event analyses with censoring, Kaplan-Meier method was used, while for multivariate analysis, Cox proportional-hazards model was used. $P \leq 0.05$ was considered statistically significant. Statistical analysis were performed using SPSS 20.0 while PFS and OS graphs was prepared using Graphpad Prism 8.0.

RESULTS

Patients and disease characteristics

The median age was 60 years (range: 44 to 70 years), with males making up 77.5 % (24/31) of that age group. Most patients (62.3 %, 19/31) had symptoms of dizziness and fatigue, and some patients (33.5 %, 11/31) manifested fever, night sweats and weight loss. Four patients (12.9 %) suffered bleeding tendency, such as petechiae, ecchymoses and epistaxis.

Table 1: Baseline characteristics for treatment-naïve patients with WM in two groups

Characteristics	BCD (N=16)	RCD (N=15)	*P*-value
Age, median(range),years	54(44,70)	64(45,68)	0.096
Sex, no. (%)			
Male	13(81.2)	11(73.3)	0.671
Female	3 (18.8)	4 (26.7)	
WBC, median(range),10^9/L	6.05(3.49,9.04)	5.11(3.79, 9.31)	0.075
HB median(range),g/L	87.0(51,142)	73(49,113)	0.063
PLT median(range), 10^9/L	229(15, 465)	125(7,382)	0.477
APTT median(range),s	39.2(26.5,63.7)	39.5(26, 74.8)	0.693
PT median(range),s	13.85(10.9,16.2)	13.5(10.7,15.9)	0.452
β2-MG median(range),mg/L	3.36(1.74,6.48)	3.43(0.32,9.1)	0.906
Albumin median(range),g/L	32.0(27,41.7)	32.0(25.3,41.8)	0.464
LDH median(range),U/L	153.45(83,288)	152.0(78,329)	0.540
Serum IgM, median(range)g/L	19.65(2.44,58.36)	20.58(1.11,51.12)	0.828
IPSSWM score, NO. (%)			
Low	6(37.5)	3(20.0)	
Intermediate	4(25.0)	5(33.3)	0.561
High	6(37.5)	7(46.7)	
MYD88L265P gene, no. (%)			
MYD88^{MUT}	16(100)	15(100)	1.000
MYD88^{WT}	0	0	

Abbreviations: WBC = white blood cell; Hb = hemoglobin; PLT = platelet; APTT = activated partial thromboplastin time; PT = prothrombin time; β2-MG = β2-microglobulin; LDH = lactate dehydrogenase; IPSSWM = International Prognostic Scoring System, Waldenstrom macroglobulinemia. *P*-values pertain to differences between BCD and RCD cohorts. Baseline characteristics were not significantly different between two cohorts

Cervical adenopathy was discovered by health examination in two patients. One patient had paraprotein-related peripheral neuropathy; Three patients had the symptoms of proteinuria and one had pruritus; one patient was complicated with amyloidosis, and another one with cold agglutinin disease. All patients expressed MYD88L265P, and the CXCR4 gene was also tested in 12 patients, but was negative. The base line characteristics of the patients in the two groups are listed in Table 1.

Responses

All patients showed improvement in symptoms after treatment. In the subpopulation of interest, CT scan or type bultrasonography-defined adenopathy (≥1.5 cm) was present in 9 patients at baseline. Serial CT imaging or B-ultrasonography for five patients showed adenopathy decreased or remained stable (n = 4). One patient had a Coombs test-positive autoimmune hemolytic anemia with a baseline hemoglobin concentration of 67 g/L, and achieved MR with the hemoglobin concentration rising to 109 g/l post RCD treatment. One patient with peripheral neuropathy treated by RCD therapy kept stable disease (SD) according to the IgM, but his numbness was much better. The ORR did not show any statistically significant difference between the 2 groups (100 vs 86.6 % p = 0.226); MRRs (81.25 vs 60 %) and VGPR rates (43.75 vs 13.3 %) were higher in patients in the BCD group than in the RCD group. There were no CRs. The median time to MR in the BCD group was shorter than in the RCD group (1.3 vs 3.5 months, p = 0.026), as shown in Table 2.

Toxicities

Grade ≥ 2 treatment-related toxicities were reported in Table 3, and hematological toxicities include leukopenia, neutropenia, and thrombocytopenia. Grade 1 leukopenia and neutropenia occurred both in the BCD and the RCD group (2 v 1), and grade 4 leukopenia and neutropenia occurred only in one patient of the RCD group. Thrombocytopenia occurred only in patients in the BCD group (grades 1 – 2). The most frequent non-hematological toxicities were hypohepatia and pneumonia. Grade 1 serum bilirubin elevation occurred in two patients in the BCD group and one patient in the RCD group. Grade 3 alanine transaminase and aspartate transaminase elevation occurred in one patient in the BCD group and then declined to normality. Grade 3 pneumonia occurred both in the BCD and RCD groups (two and three patients respectively). Other toxicities include hyperglycemia, hypokalemia and hyperuricemia.

Four patients (26.6 %) in the RCD group showed a grade 1 infusion-related responses, such as fever, chilly and chest congestion. The infusion-related response usually occurred during the first cycle, and only one patient occurred during the first to fourth cycle. Bortezomib-related peripheral neuropathy occurred in 10 patients (62.5 %).

Table 2: Response rates and kinetics of response for treatment-naïve, symptomatic patients with WM in the two therapy groups

Parameter	BCD (n=16)	RCD (n=15)	*P*-value
Overall response rate, No. (%)	16(100)	13(86.6)	0.226
Major response rate, No. (%)	13(81.25)	9(60.0)	0.252
Categorical response, No. (%)			
Minor	3(18.75)	4(26.6)	0.685
Partial	6(37.5)	7(46.7)	0.722
Very good partial response	7(43.75)	2(13.3)	0.113
Median time to minor response (month)			
	1.3(1,5.5)	3.5(1,15)	0.026*

Table 3: Adverse events associated with therapy in patients with WM

Event or Abnormality	BCD (n=16) Grade, no. (%)			RCD (n=15) Grade, no. (%)		
	2	3	4	2	3	4
Leukopenia	0	0	0	0	0	1(6.7)
Neutropenia	0	0	0	0	0	1(6.7)
Thrombocytopenia	4(25)	0	0	0	0	0
Alanine transaminase elevation	0	1(6.25)	0	0	0	0
Aspartate transaminase elevation	0	1(6.25)	0	0	0	0
Pneumonia	0	2(12.5)	0	0	3(20)	0
Peripheral neuropathy	3(18.7)	0	0	0	0	0

Three patients in BCD group leaded to dosage reduction of bortezomide because of grade 2 neuropathy.

PFS and OS

With a median follow-up of 27 months (range: 4.5 to 58 months), eight and ten patients met the progression criteria in the BCD and RCD groups respectively. The median PFS in BCD and RCD group was 43 and 35 months, respectively, but no significant difference was observed (p=0.171). Four patients who died were all in the RCD group.

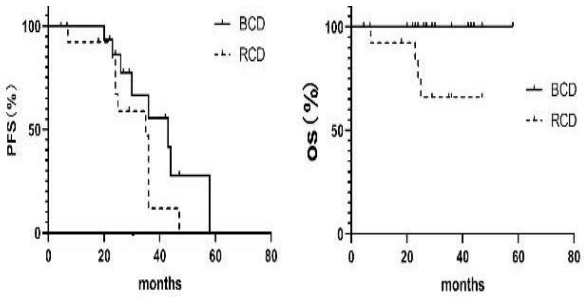

Figure 1: PFS and OS in BCD and RCD groups Except for OS in BCD and RCD groups, univariate analyses of the different levels of age, white blood cell, hemoglobin, β2-microglobulin, efficacy, IPSSWM score did not show significant differences in PFS and OS (Table 4). Age, white blood cell and different treatment regimens were not independent prognostic factors in COX regression multivariate analysis (p = 0.102, p = 0.228 and p = 0.292).

One patient who received 6 cycles of RCD died of severe pulmonary infection following disease progression. One patient developed central nervous system disease (Bing-Neel syndrome) and died, and with $CXCR4^{MUT}$ when the disease progressed. One patient died of disease progression, with a mass outside the right ventricular wall, an uncorrected heart failure as well as hyperlactacidemia. One patient who received only one cycle of RCD died of disease progression 23 months later. The estimated OS at 25 months is 100 % in the BCD group and 66.1 % in the RCD group (p = 0.033, p < 0.05; Figure 1).

DISCUSSION

Since LPL/WM is a rare non-Hodgkin lymphoma, few randomized trials have been conducted and data comparing different treatment approaches are very limited. Treatment of WM has been mostly adopted from data derived from retrospective or phase II studies [7-10]. This study is reported the efficacy of bortezomib versus rituximab plus cyclophosphamide and dexamethasone in treatment-naïve patients with waldenstrom macroglobulinemia.

Rituximab is a specific monoclonal antibody that binds to the transmembrane antigen of CD20, in order to initiate the immune apoptosis of B cells. Rituximab-based chemotherapy is the most classic and effective treatment for B-cell lymphoma, and is also one of the recommended treatments for LPL/WM, especially for patients with hypocytosis and organomegaly. In one study, the ORR of monotherapy of rituximab was 52.5 %.

Table 4: Different variables in PFS and OS of patients with WM

Variable		n	2-year PFS	Median PFS (months)	*P*-value	2-year OS	*P*-value
Age, year	≥60	16	0.705	30	0.193	0.783	0.062
	<60	15	0.839	43		1.00	
White blood cell, 10^9/L	≥6.0	11	0.762	36	0.374	1.00	0.146
	<6.0	20	0.767	35		0.819	
Hemoglobin, g/L	≥100	7	0.800	43	0.824	1.00	0.325
	＜100	24	0.761	36		0.853	
Platelet, 10^9/L	≥100	9	0.830	36	0.302	0.941	0.270
	<100	22	0.625	30		0.729	
Treatment group	BCD	16	0.862	43	0.171	1.0	0.033*
	RCD	15	0.671	35		0.755	
Categorical response	≥PR	22	0.825	35	0.804	0.880	0.782
	<PR	9	0.667	36		0.875	
	≥VGPR	9	0.875	43	0.264	1.00	0.166
	<VGPR	22	0.719	36		0.825	
ISSWM	Low	9	0.875	43	0.310	0.875	0.815
	Intermediate and High	22	0.721	36		0.882	
β2-microglobulin, mg/L	≤3.0	13	0.833	43	0.344	0.917	0.931
	>3.0	18	0.709	36		0.836	

In a prospective study of treatment-naïve patients with WM, treatment with rituximab/cyclophosphamide/dexamethasone (RCD) brought in an ORR of 83 % and MRR of 74 % [6]. The 2-year PFS was 67 %, and median PFS was 35 months for all evaluable patients. In another retrospective study of 50 untreated patients with WM receiving RCD treatment [7] , the median PFS was 34 months and the ORR was 96 %, which is similar to the results of this study. In this study, the main hematologic toxic in RCD group were grade 4 leukopenia and neutropenia (6.7 %), which is lower than previously reported (9 %).

The leukocyte and neutrophil of the patients were recovered rapidly after using G-CSF without leading to serious infection. The rate of infusion reaction of rituximab is 26.6 %, which is a little higher than the 20 % reported earlier. Most of the infusion reactions are grade 1, and occurred during the first two cycles of RCD. None of the patients stopped treatment because of infusion reaction.

Bortezomib is a selective proteasome inhibitor used to treat various hematopoietic tumors, such as multiple myeloma, marginal zone lymphoma and mantle cell lymphoma, and may have a synergistic effect with other agents [8] . Most LPL/WM patients have mutations in MYD88 gene of the BCR pathway (90 - 95 %), which phosphorylates with BTK kinase to recruit a series of cytokines that activate NF-κB pathway in order to induce cell dysplasia. The proteasome inhibitor of bortezomib plays an anti-cancer effect role by downregulating cyclin and apoptosis pathways, or inhibiting the NF-κB pathway.

In a phase II study in newly diagnosed patients with WM treated with of weekly bortezomib plus rituximab, 44 % of whom were previously untreated, showing an ORR of 78 %, with major responses observed in 44 % of patients [9]. Another phase II study of weekly bortezomib plus rituximab in newly diagnosed patients with WM reported an ORR of 88 %, including a major response of 65 % [10, 11]. The estimated 1-year PFS in this study was 79 %. In the treatment of BCD group, MRR was 81.25 %, with very good partial response (VGPR) observed in 43.75 % of the patients.

The median PFS in BCD group was 43 months with an estimated PFS of 77.5 % at 26 months. The response and PFS are better than in RCD group, although the difference is not significant. Neuropathy is a most frequent toxicity observed with bortezomib-based therapy. The incidence rate was 62.5 % compared to 75 % reported earlier, while the grade 2 rate was 18.5 %, leading to the reduction in bortezomib. Thus, if a patient has a neuropathy related to the monoclonal process, bortezomib-based regimen is not recommended as the first choice.

There was a high ORR (100 vs 86.6 %) and MRR (81.25 % v 60 %) in both groups in the study. The median time to minor response in the BCD group was 1.3 months, which is similar to the 1.4 months reported[12], and superior to the 3.5 months in the RCD group. Transient increases in IgM titers (also known as the IgM flare) [13] have been found in 60 % of patients after rituximab monotherapy initiation, circumstances in which rituximab has been used in combination therapy also included. Rituximab-based combination chemotherapy may reduce the incidence of IgM flare. Serum IgM level was elevated transiently in two patients in RCD group (no more than 25 %, and no symptoms of hyperviscosity) after initiating therapy, which may result in a slower response of the RCD group. Therefore, for patients with a high level of IgM or hyperviscosity who require reduction of tumor burden, bortezomib-based regimen may be considered.

Age, IPSSWM score, leukocyte, hemoglobin, platelet count and therapeutic effect had no effect on PFS or OS in the present study. The median PFS was longer in BCD group but not significantly different from that of RCD group. Four cases of death all occurred in RCD group, which is significantly different from BCD group. However, therapy-regimen was not an independent prognostic factor after being included in multivariate analysis. All death cases occurred in patients over 60 years old. In combination with WM International Prognostic Scoring System, age may be a non-ignorable confounder. No significant difference was found between tBCD and RCD groups in patients over 60 years old, suggesting that BCD may have survival benefits. Therefore, bortezomib plus cyclophosphamide and dexamethasone may be regarded as a first-line preferred regimen for untreated patients with WM.

CONCLUSION

Either bortezomib or rituximab plus cyclophosphamide and dexamethasone are effective and safe in treatment-naïve patients with WM. However, BCD regimen has a better response time than RCD regimen and hence higher survival benefits, and therefore may be suitable for patients who need rapid reduction of tumor burden. However, further clinical trials are required to validate these findings.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors contributed to the study conception and design. Material preparation and the experiments were performed by Jingjing Shang, Xiaolan Shi and Lingzhi Yan. Data collection and analysis were performed by Song Jin, Yin Yao, Jing Wang, Weiqin Yao and Zhi Yan. The first draft of the manuscript was written by Depei Wu and Chengcheng Fu, and all authors commented on previous versions of the manuscript. Jingjing Shang, Xiaolan Shi and Lingzhi Yan contributed equally to the work and should be considered co-first authors. All authors read and approved the final manuscript.

REFERENCES

1. *Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011; 117(19): 5019-5032.*
2. *Association WM. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization 2001; 79(4): 373.*
3. *Morel P, Duhamel A, Gobbi P, Dimopoulos MA, Dhodapkar MV, McCoy J, Crowley J, Ocio EM, Garcia-Sanz R, Treon SP, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood 2009; 113(18): 4163-4170.*
4. *Treon SP, Gertz MA, Dimopoulos M, Anagnostopoulos A, Blade J, Branagan AR, Garcia-Sanz R, Johnson S, Kimby E, Leblond V, et al. Update on treatment recommendations from the Third International Workshop on Waldenstrom's macroglobulinemia. Blood 2006; 107(9): 3442-3446.*
5. *Treon SP, Merlini G, Morra E, Patterson CJ, Stone MJ. Report from the Sixth International Workshop on Waldenström's Macroglobulinemia. Clin Lymphoma Myeloma Leuk 2011; 11(1): 68-73.*
6. *Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Zervas K, Tsatalas C, Kokkinis G, Repoussis P, Symeonidis A, Delimpasi S, Katodritou E, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol 2007; 25(22): 3344-3349.*
7. *Paludo J, Abeykoon JP, Kumar S, Shreders A, Ailawadhi S, Gertz MA, Kourelis T, King RL, Reeder CB, Leung N, et al. Dexamethasone, rituximab and cyclophosphamide for relapsed and/or refractory and treatment-naïve patients with Waldenstrom macroglobulinemia. Br J Haematol 2017; 179(1): 98-105.*
8. *Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, Sheehy P, Manning RJ, Patterson CJ, Tripsas C, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med 2012; 367(9): 826-833.*
9. *Chen CI, Kouroukis CT, White D, Voralia M, Stadtmauer E, Stewart AK, Wright JJ, Powers J, Walsh W, Eisenhauer E. Bortezomib is active in patients with untreated or relapsed Waldenstrom's macroglobulinemia: a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007; 25(12): 1570-1575.*
10. *Dimopoulos MA, García-Sanz R, Gavriatopoulou M, Morel P, Kyrtsonis MC, Michalis E, Kartasis Z, Leleu X, Palladini G, Tedeschi A, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab*

(BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood 2013; 122(19): 3276-3282.

11. *Treon SP, Ioakimidis L, Soumerai JD, Patterson CJ, Sheehy P, Nelson M, Willen M, Matous J, Mattern J, 2nd, Diener JG, et al. Primary therapy of Waldenström macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J Clin Oncol 2009; 27(23): 3830-3835.*
12. *Treon SP, Hunter ZR, Matous J, Joyce RM, Mannion B, Advani R, Cook D, Songer J, Hill J, Kaden BR, et al. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03-248. Clin Cancer Res 2007; 13(11): 3320-3325.*
13. *Gertz MA, Rue M, Blood E, Kaminer LS, Vesole DH, Greipp PR. Multicenter phase 2 trial of rituximab for Waldenström macroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). Leuk Lymphoma 2004; 45(10): 2047-2055.*