Light chain amyloidosis associated with Waldenström macroglobulinemia: treatment and survival outcomes

Light chain (AL) amyloidosis is an uncommon clinical manifestation of Waldenström macroglobulinemia (WM), an IgM-secreting lymphoplasmacytic lymphoma characterized by recurrent mutations in *MYD88* and *CXCR4*. WM-associated AL (WM-AL) amyloidosis is distinct from typical AL amyloidosis not only because of its underlying lymphoplasmacytic neoplastic clone, but also because of the absence of t(11;14) and higher rates of soft tissue, lymph node, lung, and peripheral nerve involvement.[1,2] The occurrence of WM-AL amyloidosis confers a worse prognosis in WM patients,[3] and the management approach is not standardized. Commonly used treatment regimens are derived from those used in WM without concurrent AL amyloidosis or in typical AL amyloidosis with a pure plasma cell neoplastic clone.[4-6] Here we describe the treatment and survival outcomes of a cohort of patients with WM-AL amyloidosis.

We identified consecutive patients with WM-AL amyloidosis evaluated at the Boston University Amyloidosis Center between 2006 and 2022. All patients met consensus clinicopathological criteria for a diagnosis of WM (i.e., presence of a serum IgM paraprotein and bone marrow infiltration by lymphoplasmacytic lymphoma of any extent)[7] and had positive Congo red staining of a biopsy specimen with typing confirming AL amyloidosis. The amyloidogenic protein was typed by immunohistochemistry, immunogold electron microscopy, or liquid chromatography and tandem mass spectrometry. Hematologic and organ responses to treatment for AL amyloidosis and WM were assessed using consensus definitions.[8,9] Event-free survival was defined as the time between the diagnosis of WM-AL amyloidosis among treated patients and next line of treatment or death, whichever occurred first. Overall survival was defined as the time between the diagnosis of WM-AL amyloidosis and death from any cause or last follow-up. Logistic regression models were fitted to identify predictors of hematologic response. Time-to-event outcomes were calculated using the Kaplan-Meier method, and the log-rank test was used to compare estimates between groups. The Cox-proportional hazard regression method was used to fit models for event-free and overall survival. *P* values <0.05 were considered statistically significant.

The study cohort consisted of 49 patients with WM-AL amyloidosis. Ten patients (20%) were diagnosed simultaneously with WM and AL amyloidosis. In the remaining 39 patients (80%) AL amyloidosis was diagnosed after WM, with a median time to diagnosis of 3 months (range, 0-201); 12 patients (24%) were diagnosed with AL amyloidosis more than 5 years after the diagnosis of WM. Eight patients (16%) received a median of two WM-directed therapies (range, 1-4) before the diagnosis of AL amyloidosis. The patients' baseline clinical characteristics at the time of WM-AL amyloidosis diagnosis are shown in Table 1. The presenting symptoms were heterogeneous and included peripheral edema (n=14; 29%), dyspnea (n=8; 17%), paresthesia (n=7; 14%), syncope (n=5; 10%), pleural effusion (n=5; 10%), diarrhea (n=4; 8%), foamy urine (n=4; 8%), carpal tunnel syndrome (n=3; 6%), atrial fibrillation (n=3; 6%), acute kidney injury (n=3; 6%), periorbital ecchymosis (n=2; 4%), macroglossia (n=2; 4%), lymphadenopathy (n=2; 4%), and subcutaneous mass (n=2; 4%).

Forty-four patients (90%) received at least one treatment after the diagnosis of WM-AL amyloidosis; five patients did not receive treatment due to poor performance status and/or patients' preference (Table 2). Hematologic response assessments using serum free light chain (FLC) and IgM levels were available for 43 of 44 patients. Based on FLC criteria, the overall, complete, very good partial, and partial response rates were 77%, 26%, 26%, and 26%, respectively. Based on IgM criteria, the overall, complete, very good partial, partial and minor response rates were 86%, 26%, 26%, 27%, and 7%, respectively. There was discordance between the categories of FLC and IgM responses (partial response or better) in six of 43 patients (14%); three patients had deeper category responses by IgM criteria, while another three patients had deeper category responses by FLC criteria. No baseline clinical factors were associated with achieving a hematologic complete or very good partial response by either FLC or IgM criteria (*P*>0.05 for all comparisons). Cardiac, renal, and hepatic organ response rates were 67% (n=6/9), 52% (n=12/23), and 67% (n=2/3), respectively. Patients with a hematologic complete or very good partial response had significantly higher organ response rates by both FLC criteria (78% *vs*. 17%; *P*=0.002) and IgM criteria (83% *vs*. 9%; *P*<0.001).

After a median follow-up of 2.6 years (95% confidence interval [95% CI]: 1.6-5.2), 21 patients (43%) had died. The median event-free survival was 4.9 years (95% CI: 2.3-not reached [NR]), and the estimated 5-year event-free survival rate was 48% (Figure 1A). The median overall survival was 7.3 years (95% CI: 5.4-NR), and the estimated 5-year OS rate was 70% (Figure 1B). A baseline serum creatinine >2.0 mg/dL was independently associated with both a shorter event-free survival (0.7 *vs*. 6.1 years; hazard ratio [HR]=4.20, 95% CI: 1.51-11.7; *P*=0.003) and a shorter overall

Table 1. Baseline clinical characteristics at the time of diagnosis of AL amyloidosis in patients with Waldenström macroglobulinemia.

Patients' characteristics	All patients (N=49)
Age, years Median (range) >65 years, N (%)	 68 (56-86) 30/49 (61)
Sex, N (%) Male Female	 27/49 (55) 21/49 (45)
Light chain isotype, N (%) Kappa Lambda	 19/49 (39) 30/49 (61)
Hemoglobin level, g/dL Median (range) ≤11.5 g/dL, N (%)	 12.4 (9.2-18.1) 13/48 (27)
Platelet count, x10^9/L Median (range) ≤100 x10^9/L, N (%)	 263 (126-652) 0/48 (0)
β_2-microglobulin, mg/L Median (range) >3 mg/L, N (%)	 3.2 (1.6-22.2) 26/48 (54)
Serum IgM level, mg/dL Median (range) >4,000 mg/dL, N (%)	 1418 (284-5,498) 6/49 (12)
dFLC, mg/L Median (range) >180 mg/L, N (%)	 73.7 (5.1-1,333.5) 10/49 (20)
BM involvement by LPL, % Median (range) >10%, N (%)	 20 (10-60) 41/48 (85)
Tumor genotype, N (%) *MYD88* mutation *CXCR4* mutation t(11;14)	 17/21 (81) 3/9 (33) 0/27 (0)
Serum creatinine, mg/dL Median (range) >2.0 mg/dL, N (%)	 0.9 (0.5-4.9) 7/48 (15)
Urine protein excretion, mg/24 h Median (range) >5,000 mg/24 h, N (%)	 655 (0-14,064) 13/48 (27)
Alkaline phosphatase, IU/L Median (range) >150 IU/L, N (%)	 91 (36-924) 8/47 (17)
Brain natriuretic peptide, pg/mL Median (range) >81 pg/mL, N (%)	 77 (3-2,163) 23/48 (48)
NT-pro-BNP, pg/mL Median (range) >332 pg/mL, N (%)	 554 (62-5,732) 13/22 (59)
Troponin I, ng/mL Median (range) >0.1 ng/mL, N (%)	 0.012 (0.006-0.599) 4/48 (8)
BU cardiac stage, N (%) I II III	 25/48 (52) 19/48 (40) 4/48 (8)
IPSSWM stage, N (%) Low Intermediate High	 12/48 (25) 31/48 (65) 5/48 (10)
Organ involvement, N (%) Renal Cardiac Peripheral nervous system Autonomic nervous system Gastrointestinal Lymph node Pulmonary Skin/soft tissue Hepatic	 25/49 (51) 17/49 (35) 16/49 (33) 10/49 (20) 8/49 (16) 8/49 (16) 7/49 (14) 7/49 (14) 3/49 (6)

dFLC: difference between involved and uninvolved serum free light chain; BM: bone marrow; LPL: lymphoplasmacytic lymphoma; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; BU: Boston University; IPSSWM: International Prognostic Scoring System for Waldenström macroglobulinemia.

survival (2.5 *vs*. 10 years; HR=3.91, 95% CI: 1.29-11.8; *P*=0.02) (*Online Supplementary Table S1, Online Supplementary Figure S1*). There was also a trend to shorter overall survival in patients with B-natriuretic peptide levels >81 pg/mL (5.2 *vs*. 10 years; HR=2.31, 95% CI: 0.93-5.77; *P*=0.07) (*Online Supplementary Table S1, Online Supplementary Figure S1*). Using the Boston University cardiac staging system, patients with stage I, II, and III disease had estimated 5-year overall survival rates of 81%, 61%, and 25%, respectively (*P*=0.10) (*Online Supplementary Figure S1*). The depth of hematologic FLC and IgM responses was significantly associated with both event-free and overall survival (Figure 1C-F). The median overall survival from the time of WM diagnosis was 12.8 years (95% CI: 10.8-NR).

The response and survival outcomes for each frontline treatment regimen are summarized in Table 2. Maintenance rituximab was administered to seven of 33 patients (21%) who achieved a partial response or better to a rituximab-containing frontline regimen. Among these patients, maintenance rituximab was associated with a significantly higher 5-year event-free survival rate (100% *vs*. 41%; *P*=0.02) and a trend to a higher overall survival rate (100% *vs*. 67%; *P*=0.05) (*Online Supplementary Figure S1*).

Eleven of 44 treated patients (25%) received salvage therapy, which most commonly was a bortezomib- and/or bendamustine-based regimen (*Online Supplementary Table S2*). Two patients received ibrutinib monotherapy without achieving either a hematologic or organ response. One patient was treated with venetoclax-obinutuzumab after being refractory to bortezomib, dexamethasone, and rituximab and bendamustine and rituximab, and achieved a hematologic partial response with stable proteinuria.

The occurrence of WM-AL amyloidosis is an uncommon complication that alters the natural history of WM. We observed a median overall survival of 7.3 years from the diagnosis of WM-AL amyloidosis. This survival estimate compares favorably to the median overall survival of 2.5 years published by the Mayo Clinic,[3] perhaps due to a lower frequency of cardiac involvement in our cohort of patients (35% *vs*. 57%). Both studies identified cardiac involvement as an adverse prognostic factor for overall survival, suggesting the potential relevance of the Boston University and Mayo cardiac staging systems in patients with WM-AL amyloidosis. We also identified renal dysfunction as an important prognostic factor for both event-free and overall survival. In contrast to the study by the Mayo Clinic group,[3] we included patients with <10% bone marrow involvement by lymphoplasmacytic lymphoma according to the consensus diagnostic criteria for WM.[7] This difference in study design is unlikely to explain the observed survival discrepancy, as bone marrow involvement by lymphoplasmacytic lymphoma (<10% *vs*. ≥10%) was not prognostic for survival. Importantly, we show that

the established response criteria for both AL amyloidosis and WM are prognostic for survival and predictive of organ response in patients with WM-AL amyloidosis.[8,9]

We also describe the timing of diagnosis of AL amyloidosis in WM patients. In most cases, AL amyloidosis was diagnosed within a few months of WM; however, 24% of patients were diagnosed more than 5 years later. This could be because of delayed recognition of the clinical syndrome of amyloidosis or because AL amyloidosis may be a late complication in some cases of WM. Nevertheless, our finding highlights the importance of monitoring for red flag symptoms of AL amyloidosis in WM patients throughout their entire disease course. In particular, cardiac AL amyloidosis should be considered in WM patients on BTK inhibitors who develop atrial fibrillation, a well-recognized side effect. In one series, approximately 8% of WM patients who developed atrial fibrillation on ibrutinib had underlying cardiac AL amyloidosis.[10] AL amyloidosis should also be considered in the differential diagnosis of IgM monoclonal gammopathy of unknown significance

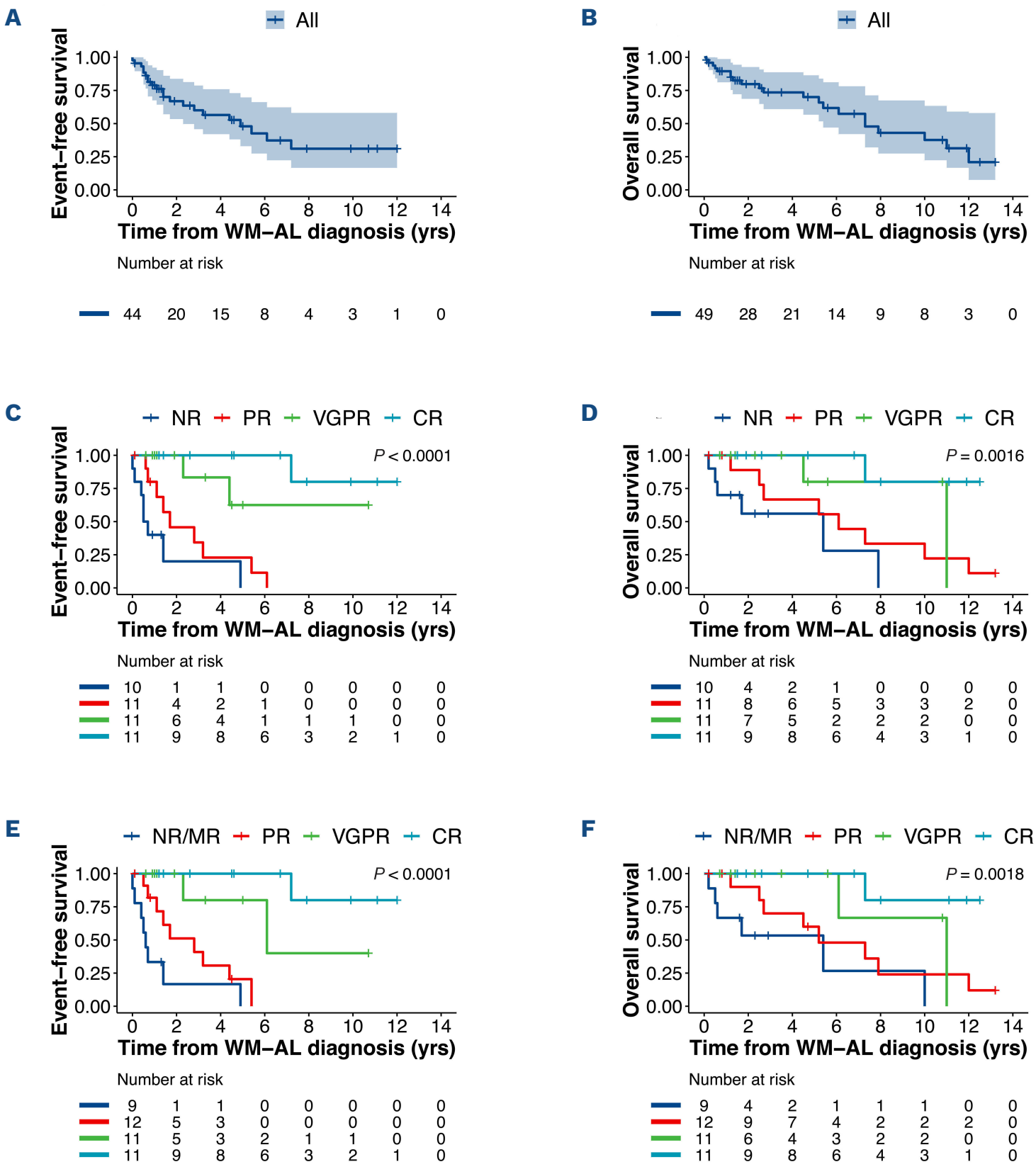

Figure 1. Survival in patients with AL amyloidosis associated with Waldenström macroglobulinemia. (A, B) Kaplan-Meier curves for event-free survival (A) and overall survival (B) for the entire cohort. (C, D) Kaplan-Meier curves for event-free survival (C) and overall survival (D) stratified by depth of free light chain response. (E, F) Kaplan-Meier curves for event-free survival (E) and overall survival (F) stratified by depth of IgM response. WM-AL: Waldenström macroglobulinemia associated with AL amyloidosis; NR: no response; PR: partial response; VGPR: very good partial response; CR: complete response; MR: minor response.

Table 2. Clinical outcomes based on the frontline regimen used for patients with AL amyloidosis associated with Waldenström macroglobulinemia.

Treatment regimen	N	FLC response N (%)		IgM response N (%)		Organ response N (%)		Survival years, median (5-year survival, %)	
		ORR (≥PR)	≥VGPR	ORR (≥PR)	≥VGPR	Cardiac	Renal	EFS	OS
Benda-R	15	12/15 (80)	8/15 (53)	15/15 (100)	10/15 (67)	3/4# (75)	5/6# (83)	5.4 (65)	7.3 (86)
BDR	9	6/9 (67)	6/9 (67)	7/9 (78)	3/9 (33)	1/2# (50)	2/6# (33)	4.4 (48)	7.3 (57)
HDM/SCT*	9	9/9 (100)	8/9 (89)	9/9 (100)	8/9 (89)	2/2# (100)	5/6# (83)	NR (88)	NR (86)
CPR	5	3/5	1/5	4/5	1/5	--	0/2#	1.7	12.0
CyBorD±R	2	2/2	0/2	2/2	0/2	--	0/2#	0.7	2.5
Melphalan	2	1/2	0/2	0/2	0/2	--	0/1#	2.8	7.7
Rituximab	1	0/1	0/1	0/1	0/1	--	--	1.3	1.6
Flu-R	1	0/1	0/1	0/1	0/1	0/1#	--	0.9	1.2

*All patients treated with high-dose melphalan and stem cell transplantation (HDM/SCT) received pre-transplant induction therapy (BDR: N=8; Benda-R: N=1). Patients treated with HDM/SCT had an estimated event-free survival of 88% at both 5 and 10 years, and there was no 100-day treatment-related mortality. #Total number of patients with involvement of the respective organ. FLC: free light chain; ORR: overall response rate; PR: partial response; VGPR: very good partial response; MR: minor response; EFS: event-free survival; OS: overall survival; NR: not reached; Benda-R: bendamustine and rituximab; BDR: bortezomib, dexamethasone, and rituximab; CPR: cyclophosphamide, prednisone, and rituximab; CyBorD±R: cyclophosphamide, bortezomib, dexamethasone, and rituximab; Flu-R: fludarabine and rituximab.

in the appropriate clinical scenario, particularly given the lower serum IgM levels we observed in patients with WM-AL amyloidosis.

Prospective data to define the optimal treatment regimen for WM-AL amyloidosis are lacking. Our findings demonstrate that standard WM regimens (such as bortezomib, dexamethasone, and rituximab or bendamustine and rituximab) can also be effective in WM-AL amyloidosis. Previous studies in which bendamustine and rituximab were given to patients with IgM-AL amyloidosis did not delineate outcomes based on the underlying neoplastic clone.[4,5] We report deep and durable responses with frontline use of high-dose melphalan and stem cell transplantation (HDM/SCT), which is typically reserved for the salvage setting in WM. HDM/SCT should be considered in selected patients with WM-AL amyloidosis, particularly since HDM/SCT can induce prolonged survival (>20 years) in typical AL amyloidosis.[11] We also observed improved event-free survival in patients given maintenance rituximab. Based on the MAINTAIN trial,[6] maintenance rituximab is not routinely used in WM but our data suggest it may have a role in WM-AL amyloidosis for patients who respond to induction therapy. Venetoclax represents a novel treatment option for WM,[12] and we present the first published case of its use in a patient with WM-AL amyloidosis. Unlike in WM, ibrutinib is associated with mixed efficacy and tolerability in WM-AL amyloidosis and must be used with caution, particularly in patients with cardiac involvement, given its pro-arrhythmic properties.[13,14] Second-generation BTK inhibitors, such as zanubrutinib, which have less cardiotoxicity than ibrutinib, warrant further investigation in WM-AL amyloidosis. Finally, there are currently no data on daratumumab in patients with WM-AL amyloidosis, but a phase II trial in WM was stopped due to futility.[15]

The limitations of the current study include the inherent selection bias associated with a non-randomized, observational study from a tertiary referral center. However, this study is the largest to date describing treatment outcomes in patients with WM-AL amyloidosis. Prospective studies are needed to optimize the management of patients with this condition.

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Data-sharing statement

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

References

1. Sidana S, Larson DP, Greipp PT, et al. IgM AL amyloidosis: delineating disease biology and outcomes with clinical, genomic and bone marrow morphological features. Leukemia. 2020;34(5):1373-1382.
2. Sissoko M, Sanchorawala V, Seldin D, et al. Clinical presentation and treatment responses in IgM-related AL amyloidosis. Amyloid. 2015;22(4):229-235.
3. Zanwar S, Abeykoon JP, Ansell SM, et al. Primary systemic amyloidosis in patients with Waldenström macroglobulinemia. Leukemia. 2019;33(3):790-794.
4. Manwani R, Sachchithanantham S, Mahmood S, et al. Treatment of IgM-associated immunoglobulin light-chain amyloidosis with rituximab-bendamustine. Blood. 2018;132(7):761-764.
5. Milani P, Schönland S, Merlini G, et al. Treatment of AL amyloidosis with bendamustine: a study of 122 patients. Blood. 2018;132(18):1988-1991.
6. Rummel MJ, Lerchenmüller C, Hensel M, et al. Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with Waldenström's macroglobulinemia (MW): results of a prospective, randomized, multicenter phase 3 study (the StiL NHL7-2008 MAINTAIN trial). Blood. 2019;134(Suppl_1):343.
7. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30(2):110-115.
8. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012;30(36):4541-4549.
9. Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. Br J Haematol. 2013;160(2):171-176.
10. Gustine JN, Meid K, Dubeau TE, Treon SP, Castillo JJ. Atrial fibrillation associated with ibrutinib in Waldenström macroglobulinemia. Am J Hematol. 2016;91(6):E312-313.
11. Gustine JN, Staron A, Szalat RE, et al. Predictors of hematologic response and survival with stem cell transplantation in AL amyloidosis: a 25-year longitudinal study. Am J Hematol. 2022;97(9):1189-1199.
12. Castillo JJ, Allan JN, Siddiqi T, et al. Venetoclax in previously treated Waldenström macroglobulinemia. J Clin Oncol. 2022;40(1):63-71.
13. Pika T, Hegenbart U, Flodrova P, Maier B, Kimmich C, Schönland SO. First report of ibrutinib in IgM-related amyloidosis: few responses, poor tolerability, and short survival. Blood. 2018;131(3):368-371.
14. Bou Zerdan M, Valent J, Diacovo MJ, Theil K, Chaulagain CP. Utility of Bruton's tyrosine kinase inhibitors in light chain amyloidosis caused by lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia). Adv Hematol. 2022;2022:1182384.
15. Castillo JJ, Libby EN, Ansell SM, et al. Multicenter phase 2 study of daratumumab monotherapy in patients with previously treated Waldenström macroglobulinemia. Blood Adv. 2020;4(20):5089-5092.