References

1. Bejar R, Stevenson KE, Caughey B, Lindsley RC, Mar BG, Stojanov P, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol. 2014;32:2691–8.
2. Lindsley RC, Saber W, Mar BG, Redd R, Wang T, Haagenson MD, et al. Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation. N Engl J Med. 2017;376:536–47.
3. Della Porta MG, Galli A, Bacigalupo A, Zibellini S, Bernardi M, Rizzo E et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. J Clin Oncol. 2016;34:3627–37, JCO673616.
4. Voso MT, Leone G, Piciocchi A, Fianchi L, Santarone S, Candoni A, et al. Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study. Ann Oncol. 2017;28:1547–53.
5. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van Loo P, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122:3616–27.
6. Yoshizato T, Nannya Y, Atsuta Y, Shiozawa Y, Iijima-Yamashita Y, Yoshida K, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. Blood. 2017;129:2347–58.
7. Craddock CF, Houlton AE, Quek LS, Ferguson P, Gbandi E, Roberts C, et al. Outcome of azacitidine therapy in acute myeloid leukemia is not improved by concurrent vorinostat therapy but is predicted by a diagnostic molecular signature. Clin Cancer Res. 2017;23:6430–40.
8. Russler-Germain DA, Spencer DH, Young MA, Lamprecht TL, Miller CA, Fulton R, et al. The R882H DNMT3A mutation associated with AML dominantly inhibits wild-type DNMT3A by blocking its ability to form active tetramers. Cancer Cell. 2014;25:442–54.
9. Balasubramanian SK, Aly M, Nagata Y, Bat T, Przychodzen BP, Hirsch CM, et al. Distinct clinical and biological implications of various DNMT3A mutations in myeloid neoplasms. Leukemia. 2018;32:550–3.
10. Jongen-Lavrencic M, Grob T, Hanekamp D, Kavelaars FG, Al Hinai A, Zeilemaker A, et al. Molecular minimal residual disease in acute myeloid leukemia. N Engl J Med. 2018;378:1189–99.
11. Winkelmann N, Schafer V, Rinke J, Kaiser A, Ernst P, Scholl S, et al. Only SETBP1 hotspot mutations are associated with refractory disease in myeloid malignancies. J Cancer Res Clin Oncol. 2017;143:2511–9.
12. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med. 2016;375:2023–36.
13. Sallman DA, Komrokji R, Vaupel C, Cluzeau T, Geyer SM, McGraw KL, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. Leukemia. 2016;30:666–73.

Leukemia (2019) 33:790–794
https://doi.org/10.1038/s41375-018-0286-7

Lymphoma

Primary systemic amyloidosis in patients with Waldenström macroglobulinemia

Saurabh Zanwar[1] · Jithma P. Abeykoon[1] · Stephen M. Ansell[1] · Morie A. Gertz[1] · Angela Dispenzieri[1] · Eli Muchtar[1] · Surbhi Sidana[1] · Nidhi Tandon[1] · S. Vincent Rajkumar[1] · David Dingli[1] · Ronald Go[1] · Martha Q. Lacy[1] · Taxiarchis Kourelis[1] · Thomas E. Witzig[1] · David Inwards[1] · Francis Buadi[1] · Wilson Gonsalves[1] · Thomas Habermann[1] · Patrick Johnston[1] · Grzegorz Nowakowski[1] · Robert A. Kyle[1] · Shaji Kumar[1] · Prashant Kapoor[1]

Received: 11 July 2018 / Revised: 22 August 2018 / Accepted: 24 September 2018 / Published online: 12 October 2018

Waldenström macroglobulinemia (WM) is a unique IgM-associated, indolent lymphoma with at least 10% marrow lymphoplasmacytic infiltrate [1]. IgM paraprotein is implicated in 5–7% of patients with light and/or heavy chain immunoglobulin amyloidosis (AL/AHL) [2–4]. However, data regarding AL/AHL in WM are sparse. A greater clonal bone marrow plasma cell (BMPC) burden confers poorer survival in AL, as observed in a study from our institution (median 16 months for patients with >10% BMPCs versus 46 months), underscoring the importance of the degree of

✉ Prashant Kapoor
kapoor.prashant@mayo.edu

[1] Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Table 1a Characteristics of WM patients with and without AL/AHL

Clinical parameters	WM without AL/AHL ($n = 922$)	WM with synchronous AL/AHL ($n = 40$)	WM with subsequent AL/AHL ($n = 35$)	p Value
Median age in years, (range)	65 (31–93)	65 (50–79)	63 (38–78)	0.24
Gender (% males)	65	65	63	0.97
Constitutional symptoms at WM diagnosis (%)	58	61	50	0.67
Lymphadenopathy at WM diagnosis (%)	20	32	22	0.24
Splenomegaly at WM diagnosis (%)	10	3	22	**0.03**
Symptomatic hyperviscosity (%)	14	2.5	6	**0.02**
Cryoglobulinemia (%)	17	0	10	0.17
Disease transformation (%)	9	3	3	0.12
Central nervous system involvement (%)	1.5	0	0	0.33
Organ involvement by amyloidosis				
Cardiac (%)	NA	61	54	0.63
Renal (%)	NA	55	54	1.0
Lymph nodes (%)	NA	32	6	**0.007**
Liver (%)	NA	18	18	1.0
Gastrointestinal (%)	NA	21	15	0.55
Nerves (%)	NA	17	21	0.77
Skin/soft tissue (%)	NA	18	14	0.76
Lung (%)	NA	10	6	0.67
Laboratory parameters at diagnosis of WM, median (range)				
Hemoglobin (g/dL)	10.6 (3.5–16.1)	12.3 (4.8–17.9)	11.5 (8.6–13.5)	**0.0004**
Platelet count (10^9/L)	220 (7–1222)	284 (144–473)	260 (92–355)	**0.01**
Beta 2 microglobulin (μg/mL)	3.2 (0.9–34.1)	3.5 (1.4–16.7)	3.3 (2.9–8.8)	0.46
Serum LDH (U/L)	141 (35–1053)	145.5 (99–325)	178 (154–217)	0.48
Serum IgM (mg/dL)	3200 (68–14,400)	2510 (147–7840)	2350 (705–13900)	0.21
Serum M protein (g/dL)	2.1 (0.1–11.6)	1.9 (0.3–5.7)	1.7 (0.7–4.45)	0.12
Urine M protein (mg/24 h)	63 (0–5150)	68 (0–545)	79 (25–167)	0.86
Involved FLC value	8.4 (0.17–7570)	32.6 (1.5–547)	54.5 (22.9–1016)	**0.002**
Lambda light chain involved (%)	19	58	50	**<0.0001**
FLC ratio, involved/uninvolved	7.7 (0.7–1818)	13.2 (2.9–1010)	93.1 (11.5–496)	**0.004**
Serum IgG (mg/dL)	624 (13–6540)	524 (17–2560)	638 (383–1730)	0.36
Serum IgA (mg/dL)	60 (4–4200)	61 (10–1710)	51 (29–346)	0.93
Bone marrow involvement by LPL (%)	50 (10–100)	30 (10–90)	40 (10–90)	**0.04**
$MYD88^{L265P}$ mutation positive, n (%)	210/257 (82)	8/10 (80)	1/3 (33)	0.19

The text in bold represents a significant difference between the groups

marrow infiltration at diagnosis [5]. Through this study, we attempted to address the impact of AL/AHL on the clinical course of WM and vice versa.

Following Institutional Review Board approval, records of WM patients seen at Mayo Clinic, Rochester between January 1, 1996 and June 30, 2017 were reviewed. We excluded all patients with WHO-defined IgM monoclonal gammopathy of undetermined significance (MGUS) [<10% marrow (lympho)plasmacytosis] [6]. A more recent (January 2006–December 2015) cohort of AL patients without WM (non-IgM AL), but with ≥10% BMPCs evaluated within 90 days of diagnosis of AL was selected for comparison with a contemporaneous cohort of WM patients with concurrent AL/AHL. Hematologic response and organ response to frontline therapy for AL/AHL were assessed by Consensus criteria [7]. Nonevaluable patients [difference in free light chain (dFLC) < 5 mg/dL] at therapy initiation were analyzed separately. Overall survival (OS) for WM was calculated from the diagnosis of WM until death or last follow-up. Amyloidosis-specific survival was calculated from the diagnosis of AL/AHL until death due to AL/AHL or last follow-up. All time-to-event endpoints were analyzed using the Kaplan–Meier method and compared by log-rank tests.

Table 1b First-line treatments for patients with WM without AL/AHL and for WM with AL/AHL

Frontline treatment, %	WM without AL/AHL ($n = 922$)	AL/AHL in WM ($n = 75$)
Rituximab-alkylator based combination	26	42
Bortezomib-based combination	4	18
Alkylator ± steroids	30	13
ASCT	0	12
Rituximab ± steroids	34	7
Others	5	8
Median lines of therapy (range)	2 (0–11)	1.5 (0–6)

ASCT autologous stem cell transplant; *NA* not applicable; *FLC* free light chain; *LPL* lymphoplasmacytic lymphoma cells; *AL/AHL* systemic light and/or heavy chain immunoglobulin amyloidosis

Univariate analyses (UVA) and multivariate analyses (MVA) using Cox regression were performed to identify the prognostic factors for amyloidosis-specific survival. For identifying the predictors of subsequent development of AL/AHL, cohorts with WM alone and WM with subsequent AL/AHL were compared using Kruskal–Wallis and two-tailed Fisher's exact test for continuous and categorical variables, respectively. The optimal cutoffs for continuous variables were obtained using receiver operating characteristics (ROC) curve analysis. Variables that were significantly different ($p < 0.05$) between the two groups were incorporated in a logistic regression analysis.

Of 997 WM patients, 75 (7.5%) had coexisting AL/AHL. In 40 (53%) patients, AL/AHL was diagnosed concurrently with WM (AL/AHL established within 2 months of the diagnosis of WM), whereas 35 (47%) patients developed it subsequently at a median duration of 2.7 years (95% CI: 1.3–4.5 years) from the diagnosis of WM. Of 32 patients with mass-spectroscopy data, 26 had AL and 6 had AHL. Table 1a outlines the clinical and laboratory features. Patients in the WM cohort had marrow lymphoplasmacytic infiltration of ≥10% while the comparator AL cohort without WM had ≥10% BMPCs. Of 75 patients with AL/AHL, 68 (91%) had initial evaluation pertaining to AL/AHL-related symptoms; three patients presented with lymphadenopathy demonstrating lymphoplasmacytic infiltrate plus amyloid deposits, while in four patients evaluated for WM-related symptoms AL/AHL was incidentally diagnosed.

The median follow-up of the entire cohort of WM patients was 8.8 years (95% CI: 8.1–9.6). The median OS from the diagnosis of AL/AHL in patients with WM ($n = 75$) was 2.5 years (95% CI: 1.6–4.2 years). The WM patients with synchronous AL/AHL had inferior OS [median 2.5 years (95% CI: 1.4–4.2 years)] compared to WM without AL/AHL [median 12.1 years (95% CI: 11.1–13.2 years); hazard ratio (HR) 5.9 (95% CI: 3.9–8.5), $p < 0.0001$, Fig. 1a]. No survival difference was noted in non-IgM AL/AHL patients with ≥10% BMPCs ($n = 605$) compared to the contemporaneous (2006–2015) cohort of WM patients ($n = 29$) with AL/AHL at diagnosis [median 2.4 years (95% CI: 1.7–3.6 years) versus 2.9 years (95% CI: 1.4–4.2 years), respectively; HR 0.9 (95% CI: 0.6–1.5), $p = 0.70$, Fig. 1b].

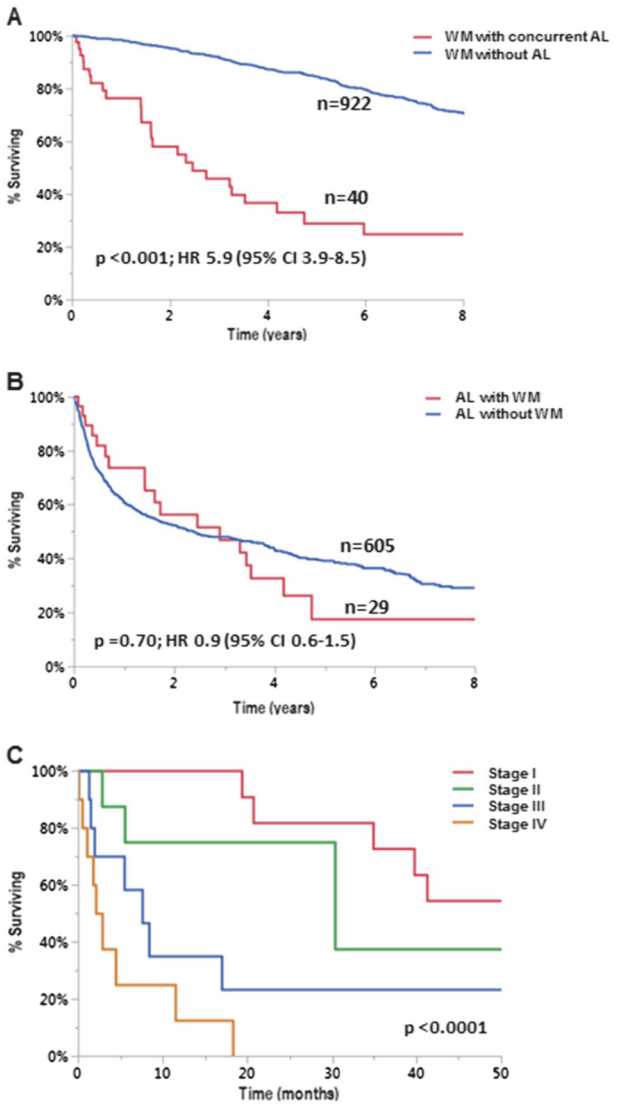

Fig. 1 **a** Overall survival of WM patients with synchronous AL/AHL was inferior [median 2.5 years (95% CI: 1.4–4.2 years)] compared to WM patients without AL/AHL [median 12.1 years (95% CI: 11.1–13.2 years); hazard ratio (HR) 5.9 (95 % CI: 3.9–8.5), $p < 0.0001$]. **b** No survival difference in OS was noted in AL/AHL patients with ≥10% BMPCs, but without associated WM ($n = 605$) compared to the contemporaneous (2006–2015) cohort of WM patients ($n = 29$) with AL/AHL at diagnosis [median 2.4 years (95% CI: 1.7–3.6 years) versus 2.9 years (95% CI: 1.4–4.2 years), respectively; HR 0.9 (95% CI: 0.6–1.5), $p = 0.70$]. **c** Overall survival based on 2012 Mayo Staging System for AL. The median OS for Mayo 2012 stage 1 ($n = 12$), stage 2 ($n = 9$), stage 3 ($n = 10$), and stage 4 ($n = 10$) was 79.5, 30, 7.5, and 2.5 months, respectively ($p < 0.0001$)

A UVA for amyloidosis-specific survival was conducted using the following variables at diagnosis of AL/AHL in WM: age, gender, *MYD88*^{L265P} status, marrow lymphoplasmacytosis, FLC subtype, involved FLC (iFLC), involved to uninvolved FLC ratio (FLCR), elevated β_2-microglobulin (β_2M; >2.7 µg/dL), low albumin (<3.5 g/dL), hemoglobin, platelets, and individual organ involvement. Age ($p = 0.002$), cardiac involvement ($p < 0.001$), gastrointestinal tract involvement ($p = 0.02$), elevated β2M ($p = 0.002$), and low albumin ($p = 0.008$) emerged as prognostic markers. On MVA, cardiac involvement [risk ratio (RR) 2.8 (95% CI: 1.1–8.6); $p = 0.03$] and low albumin [RR 3.4 (95% CI: 1.4–10.5); $p = 0.007$] were independent prognosticators. The Revised Mayo 2012 staging system for AL was applicable to this cohort (Fig. 1c).

Of 75 patients with coexisting AL/AHL, 60 (83%) patients received systemic therapy targeting the lymphoplasmacytic clone; 12 had poor performance status and therapy-related data were unavailable in three (Table 1b). In the WM cohort that subsequently developed AL/AHL ($n = 35$), 29% had smoldering WM and were treatment-naive prior to the diagnosis of AL/AHL. Among evaluable patients with data available for response-assessment ($n = 21$), partial response (PR) or very good PR (VGPR) was achieved in 57% (PR = 28.5%, VGPR = 28.5%), with no response in 9 (38%) and progression observed in one patient. Among the 12 patients with dFLC < 5 mg/dL at diagnosis of AL ($n = 12$), response-assessment data were available in 8 patients, 6 (75%) of whom achieved a dFLC < 1 mg/dL after initial therapy. Organ response data were available for cardiac ($n = 25$), renal ($n = 20$), and hepatic involvement ($n = 6$), with 12%, 25%, and 0% demonstrating cardiac, renal, and hepatic response, respectively to treatment. On UVA, using variables significantly different in the WM with or without AL cohorts (Table 1a), only iFLC ($p = 0.007$) level and FLCR ($p = 0.008$) at diagnosis of WM were found to be associated with the development of AL/AHL in WM subsequently. Using the cutoffs of iFLC ≥ 25 mg/dL and FLCR ≥ 10 obtained on ROC curve analysis, a MVA involving these two variables was performed among the subset of patients in whom data for FLC at diagnosis of WM was available ($n = 269$; 263 in WM without AL/AHL cohort and 6 in WM with subsequent AL/AHL cohort). On MVA, FLCR ≥ 10 remained independently associated with the subsequent development of AL/AHL ($p = 0.01$).

IgM amyloidosis is a distinct entity with unique prognostic features [8]. AL/AHL is historically associated with worse outcome than WM [9, 10]. Median survival for patients with isolated WM in our cohort was 12 years. By contrast, in a prior study median OS approached 12 years for select AL patients undergoing ASCT (4-year OS: 65–91%) and merely 12 months in the non-ASCT population (4-year OS: 16–32%) [10]. However, the outcomes associated with the coexistence of these two disorders are not well-established. Our study has three key findings: (1) concurrent presence of WM does not impact the outcome of patients with AL/AHL amyloidosis, i.e., OS of WM-associated and non-WM AL/AHL is comparable. (2) The coexistence of AL/AHL, in contrast, negatively impacted outcome of WM patients, and OS of such patients is markedly inferior (median 2.5 years) to that of WM patients without AL/AHL (median 12.1 years). (3) FLCR ≥ 10 at diagnosis of WM is independently predictive of developing AL/AHL subsequently.

The development of AL/AHL represents an important deflection point in the natural history of WM. A likely explanation for lower amyloidosis-specific survival in our cohort (median 2.5 years) compared to other studies reporting a survival range of 44–76 months for IgM AL patients [3, 4, 11], including the recent European collaborative study by Sachchithanantham et al. [8], is that our study had evaluated only WM patients and excluded patients with <10% marrow infiltration.

Cardiac involvement and low albumin at AL/AHL diagnosis were independent unfavorable predictors of survival, an observation consistent with the findings of previous IgM AL related studies [3, 11]. The Revised Mayo 2012 staging correlated well with OS from the diagnosis of AL/AHL in WM patients as the prognosis in these patients was primarily driven by concurrent AL/AHL [12]. Only 18% (95% CI: 11–29%) of evaluable patients with WM and AL/AHL underwent ASCT during their disease course in our study, comparable to the approximately one-fifth of patients with AL/AHL that are typically eligible for ASCT.

Often, symptoms such as fatigue or dyspnea are attributed to WM-related anemia or chemotherapy, and a subtle cardiac involvement by AL/AHL may be overlooked. Therefore, we attempted to identify any coexisting clues that could aid in raising the suspicion of AL/AHL. In our study, a FLCR ≥ 10 was associated with development of AL/AHL subsequently during the course of WM. A study assessing the pre-diagnosis sera of patients with AL found that the dFLC was higher in AL cases compared to healthy controls and preceded the development of AL by up to 11 years [13]. An abnormal FLCR in patients with MGUS has been associated with increased risk of progression to AL [14]. WM is infrequently associated with elevated FLCs compared to multiple myeloma or AL [15]. Our finding of FLCR ≥ 10 predicting for the development of AL/AHL is limited by incomplete data. Nonetheless, it provides the basis for heightened suspicion for future development of AL/AHL.

In summary, although AL/AHL is an uncommon complication in WM, it confers a significantly poorer survival. In contrast, the survival of AL/AHL patients with or without

associated WM appears comparable. A FLCR of ≥10 at diagnosis of WM may predict future development of AL/AHL, but this finding requires external validation. Our study draws its strength from a large size and long follow-up and provides insight into areas with previously limited data.

Acknowledgments The contribution of S.S. and M.A.G. to this study was supported, in part, by the grants from the International Waldenström Macroglobulinemia Foundation and the Amyloidosis Foundation.

Author contributions S.Z., J.P.A. and P.K. designed the study. S.Z., J.P.A. and P.K. collected analyzed and interpreted the data and wrote the first draft of the manuscript. S.M.A., A.D., M.A.G., E.M., S.S., N. T., S.V.R., D.D., R.G., M.Q.L., T.K., T.E.W., D.I., F.B., W.G., T.H., P.J., G.N., R.A. and S.K. interpreted the data, critically revised the manuscript and all authors approved the final version.

Compliance with ethical standards

Conflict of interest Dr. Ansell has received research funding from Bristol-Myers Squibb, Celldex, Merck, and Seattle Genetics. Dr. Dispenzieri has received research funding from Prothena, Jannsen, Pfizer, GSK, Takeda, Alnylam, Celgene, and serves on the advisory board for Takeda and Intellia. Dr. Gertz has received funding from Amgen, Prothena, Annexon, Appellis, Johnson and Johnson, and Celgene. Dr. Kumar has received research grants for clinical trials from Celgene, Takeda, Janssen, BMS, Sanofi, KITE, Merck, Abbvie, Medimmune, Novartis, Roche-Genentech, Amgen. Dr. Leung serves on the advisory board for Takeda and Prothena. Dr. Kapoor is principal investigator on studies for which Mayo Clinic receives funding from Takeda, Sanofi, and Amgen. The remaining authors declare that they have no conflicts of interest.

References

1. Kapoor P, Ansell SM, Fonseca R, Chanan-Khan A, Kyle RA, Kumar SK, et al. Diagnosis and Management of Waldenstrom Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. JAMA Oncol. 2017;3:1257–65.
2. Gertz MA, Buadi FK, Hayman SR. IgM amyloidosis: clinical features in therapeutic outcomes. Clin Lymphoma Myeloma Leuk. 2011;11:146–8.
3. Wechalekar AD, Lachmann HJ, Goodman HJ, Bradwell A, Hawkins PN, Gillmore JD. AL amyloidosis associated with IgM paraproteinemia: clinical profile and treatment outcome. Blood. 2008;112:4009–16.
4. Palladini G, Russo P, Bosoni T, Sarais G, Lavatelli F, Foli A, et al. AL amyloidosis associated with IgM monoclonal protein: a distinct clinical entity. Clin Lymphoma Myeloma. 2009;9:80–3.
5. Kourelis TV, Kumar SK, Gertz MA, Lacy MQ, Buadi FK, Hayman SR, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. J Clin Oncol. 2013;31:4319–24.
6. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition, vol. 2. International Agency for Research on Cancer; 2017.
7. Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, Landau H, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26:2317–25.
8. Sachchithanantham S, Roussel M, Palladini G, Klersy C, Mahmood S, Venner CP, et al. European Collaborative Study defining clinical profile outcomes and novel prognostic criteria in monoclonal immunoglobulin M-related light chain amyloidosis. J Clin Oncol. 2016;34:2037–45.
9. Castillo JJ, Olszewski AJ, Kanan S, Meid K, Hunter ZR, Treon SP. Overall survival and competing risks of death in patients with Waldenstrom macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database. Br J Haematol. 2015;169:81–9.
10. Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, et al. Improved outcomes for newly diagnosed AL amyloidosis over the years 2000–2014: cracking the glass ceiling of early death. Blood. 2017;129:2111–19.
11. Terrier B, Jaccard A, Harousseau JL, Delarue R, Tournilhac O, Hunault-Berger M, et al. The clinical spectrum of IgM-related amyloidosis: a French nationwide retrospective study of 72 patients. Medicine. 2008;87:99–109.
12. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;30:989–95.
13. Weiss BM, Hebreo J, Cordaro DV, Roschewski MJ, Baker TP, Abbott KC, et al. Increased serum free light chains precede the presentation of immunoglobulin light chain amyloidosis. J Clin Oncol. 2014;32:2699–704.
14. Rajkumar SV, Kyle RA, Therneau TM, Melton LJ 3rd, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106:812–7.
15. Charafeddine KM, Jabbour MN, Kadi RH, Daher RT. Extended use of serum free light chain as a biomarker in lymphoproliferative disorders: a comprehensive review. Am J Clin Pathol. 2012;137:890–7.