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Improved Treatment Related Mortality in Patients with Primary Systemic Amyloidosis (AL Amyloidosis) undergoing Autologous Hematopoietic Stem Cell Transplant (aHSCT)

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Abstract

To date, there is no standard of care for patients with newly diagnosed Primary (AL) amyloidosis. Autologous hematopoietic stem cell transplant (aHSCT) is a reasonable option, but has been limited in its use due to increase in treatment-related mortality (TRM). We retrospectively analyzed the outcomes of 42 newly diagnosed consecutive AL amyloidosis patients transplanted at our center. The median age at aHSCT was 57.5 (range 26-71). Twenty one (50%) had involvement of at least two organs and 40 (97%) patients had cardiac stage I or II. Patients received high dose Melphalan 140(n=4) or 200(n=38) mg/m^2. Median times to neutrophil and platelet engraftments were 12 and 18 days, respectively. Three months hematologic response were complete response in 21patients (50%), very good partial response in 4 (10%), partial response in 5 (12%) and Minimal/Stable disease in 6(15%). The respective 1, 3, and 5 year progression-free survival were 79%, 67% and 57%, and overall survival from Transplant 81%, 73% and 66%. Day 100 and 1 year TRM were 4.8% and 7.1% respectively. Our results show that aHSCT is a safe and reasonable option for patients with AL amyloidosis. Day 100 and 1 year TRM compares favorably to multiple myeloma patients undergoing aHSCT.

Keywords: *Primary Amyloidosis, Transplantation, Light chain Amyloidosis, AL amyloid, amyloidosis*

Introduction

In the family of protein conformational diseases termed the "systemic amyloidosis", misfolded proteins aggregate and form fibrils that deposit in extracellular spaces throughout the body. With accumulation over time, this tissue deposition interferes with physiologic functions and results in progressive organ damage and death (1). Immunoglobulin light chain (AL), the most common form of the systemic amyloidosis, has a reported incidence of 9 cases per million persons-years (2, 3).

Currently, there is inadequate data to define a standard of care treatment for AL amyloidosis. Chemotherapy is aimed at reducing or eliminating the precursor protein, preventing misfolding and fibril formation, promoting reabsorption of deposits, and addressing markers of organ disease (1, 2). Improvements in response and overall survival have been seen with the institution of novel agent (thalidomide, lenalidomide and bortezomib)-based therapy in small prospective studies (4-8), however these responses can be short lived.

High dose chemotherapy and autologous hematopoietic stem cell transplant (aHSCT) has been shown to offer durable response in eligible patients, however its use

continues to be controversial due to high treatment-related mortality (TRM) of 10-39% (9-14). A recent retrospective review showed a superior outcome of AL amyloid patients compared to multiple myeloma (MM) patients undergoing aHSCT with an improved day 100 TRM of 8.8% (1.4% in MM patients) (15). Further improvement in TRM can be obtained by improved patient selection and supportive care. We retrospectively analyzed the outcomes of 42 newly diagnosed consecutive AL amyloidosis patients who underwent aHSCT at The Ohio State University.

Patients and Methods

Patients

Between August 1998 and April 2015, 42 consecutive patients with AL amyloidosis who had undergone aHSCT at The Ohio State University Medical Center were included in this analysis. Patients were eligible for ASCT if they had an ECOG performance status of 0-2, adequate cardiac (left ventricular ejection fraction ≥45%), pulmonary (diffusing capacity of the lung for carbon monoxide ≥50%), hepatic (bilirubin, transaminases < 2 times upper limit of normal) function and no uncontrolled infection.

Hematopoietic Stem Cell Collection

G-CSF mobilized peripheral blood progenitor cells were collected using standard mobilization protocol and apheresis techniques. All patients signed informed consent according to our institutional and the National Marrow Donor Program guidelines. The study was approved by the Institutional Review Board at The Ohio State University.

Preoperative Regimen and Supportive Care

All patients received conditioning regimen with melphalan 200mg/m^2 in split dose (100 mg/m^2 x 2 days), except for patients with CrCl <50 ml/min including patients on hemodialysis, in which case melphalan 140 mg/m^2 was given also in split dose (70 mg/m^2 x 2 days). Split dose was given to reduce GI toxicity. Patients received infection prophylaxis with antiviral (valacyclovir), antibiotic (Levaquin) and antifungal (fluconazole). Patients only received filgrastim to aid in neutrophil recovery if needed in the case of sepsis as decided by the treating physician. The reason not to give filgrastim was to reduce complications from fluid retention. Blood products were irradiated and leukopore filtered.

Engraftment, Response and Outcome

Response, relapse and disease progression were defined based on the Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis and New Criteria Response(16) (17). Initial responses were assessed at approximately 3 months post aHSCT. Neutrophil engraftment was defined as the first of 3 consecutive days with an ANC ≥ 0.5 x 10^9/L. Platelet engraftment was defined as the first of 7 consecutive days with a platelet count of ≥ 20 x 10^9/L without platelet transfusion.

Statistical Methods

We retrospectively analyzed the outcomes of 42 patients with newly diagnosed AL amyloidosis who had undergone aHSCT as part of their treatment regimen. Hematologic responses, post-transplant survival and treatment related mortality (TRM) were evaluated.

Primary endpoints were progression free survival (PFS), and overall survival from date of transplant (OS-aHSCT) and overall survival from date of diagnosis (OS-Dx). PFS was calculated from the date of transplant to the date of disease progression or death, whichever occurred first. Patients who were still disease-free were censored at the date of last observation. OS-aHSCT was determined from the date of transplant to death from any cause or the date of the last observation. OS-Dx was determined from the date of diagnosis to death from any cause or the date of last observation. Death from any cause other than relapse was classified as TRM. Survival curves were estimated using the method of Kaplan-Meier... Patient characteristics were also summarized (median and range for continuous variable, frequency for categorical variables). Survival curves were compared in the categorical variables by the log-rank tests for the univariate analysis. Cox regression models were used for continuous variables (i.e. age and KPS) for the univariate analysis. Multivariable Cox regression models were fit to OS and PFS using all the variables with $p<0.15$ in the univariate analysis. Variables with

p>0.05 were removed sequentially from the Cox regression model using backward selection method. P values < 0.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC).

Results

Patient Characteristics

The median age of the patients was 57.5 (range 26-71). Of these 24 (57%) were male and 18(43%) were female. The median Karnofsky Performance score was 80 (range 60-100). Thirty-eight patients (90.5%) received high dose Melphalan 200 mg/m^2 prior to aHSCT and the remaining received 140 mg/m^2 adjusted for comorbidities. The median number of infused CD34+ stem cells was 4.69 x 10^6 / kg. Twenty patients (50%) had involvement of at least 2 organs. Cardiac stage was I in 35 patients, II in 2 and III in 1 patient. Patient characteristics are summarized in Table 1.

Table 1. *Patient Baseline Characteristics*

Characteristic	Number (N=42)
Age (at aHSCT):	
Median	57.5
Range	26 - 71
Sex Male/Female	24/18
KPS Median (Range)	80 (60 – 100)
Prior Treatment:	
None	12 (29%)
1	23 (55%)
2	7 (17%)
Organ involved	
kidney	33 (79%)
cardiac	9 (21%)
GI	10 (24%)
Number of organs involved	
1	21 (50%)
2	11 (26%)
≥3	10 (24%)
Cardiac Stage:	
I	35 (85%)
II	5 (12%)
III	1 (2%)
unknown	1 (2%)

Engraftment

All patients achieved engraftment. Median time to neutrophil and platelet engraftment were 12(8-19) and 18(9-23) days respectively.

Hematologic Response

Hematologic response was available for 36 patients. Complete response (CR) was achieved in 21(50%) patients, very good partial response (VGPR) in 4 (10%), partial response (PR) in 5 (12%) and stable disease (SD) 6 (14%).

Treatment-Related Mortality, Progression-Free and Overall Survival

The 100 day TRM was 4.5% (2 patients: 1diffuse alveolar hemorrhage, 1 fungal infection) and the 1 year TRM was 7.1% (3 patients, 3rd patient had Stroke). The median PFS was 106.6 months (95% CI = 39.8, NA). The 1 year, 3 year and 5 year PFS rates were 79%, 67% and 57% respectively (Table 2, Figure 1). The median OS-aHSCT was 112.0 months (95% CI = 52.1, NA). The 1 year, 3 year, and 5 year OS-aHSCT rates were 81%, 73%, and 66% respectively (Table 2, Figure 2). The median OS-Dx was 117.2 months (95% CI = 60.4, NA). The 1 year, 3 year and 5 year OS-Dx were 88%, 73% and 69% respectively (Table 2, Figure 3). In the multivariate analysis, response (CR and VGPR) was highly associated with improved OS (p<0.001) and Sex (female, p=0.002) and number of prior treatment (0-1, p=0.013) were significantly associated with PFS (Table not shown).

Table 2. *Summary of Survival Rates*

	N	Censored	1 yr. survival rate (%)	3 yr. survival rate (%)	5 yr. survival rate (%)	Median (months)	95% CL (months)
PFS	42	25	79	67	57	106.6	(39.8, NA)
OS-ASCT	42	27	81	73	66	112.0	(51.2, NA)
OS-DX	42	27	88	73	69	117.2	(60.4, NA)

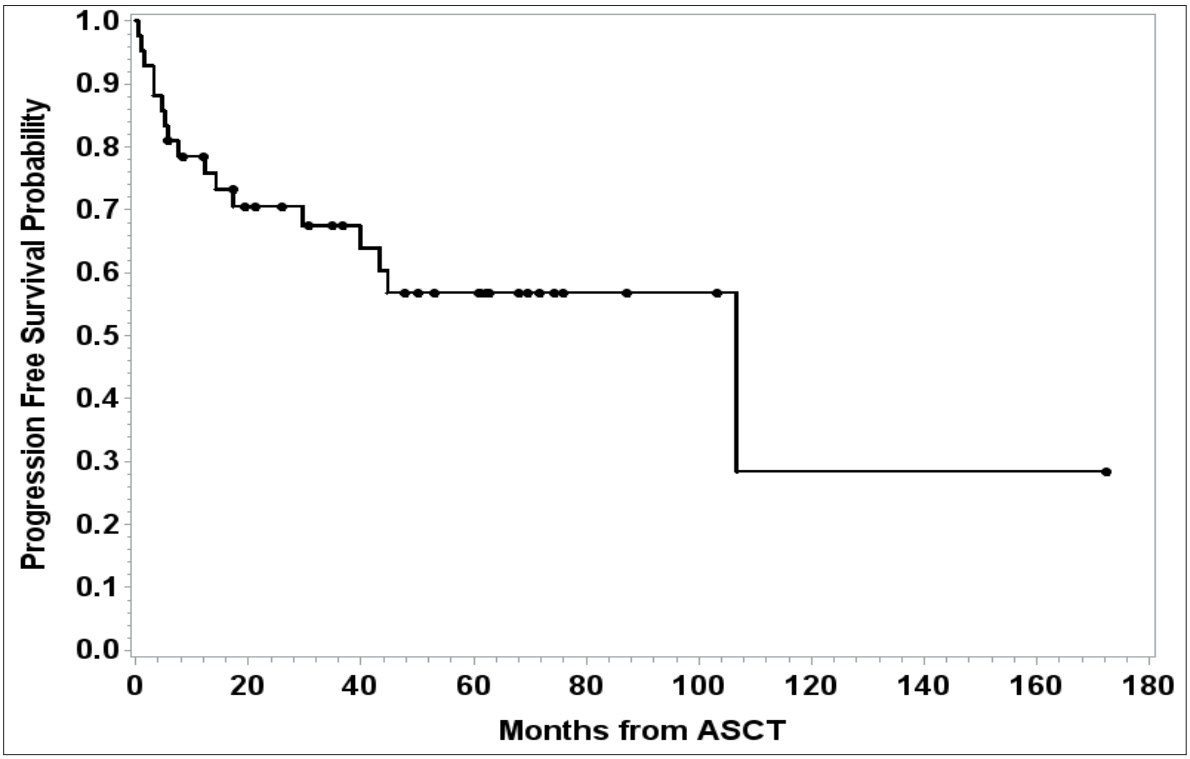

Figure 1. *Progression free survival from date of aHSCT to date of disease progression, date of death from any cause or date of last observation*

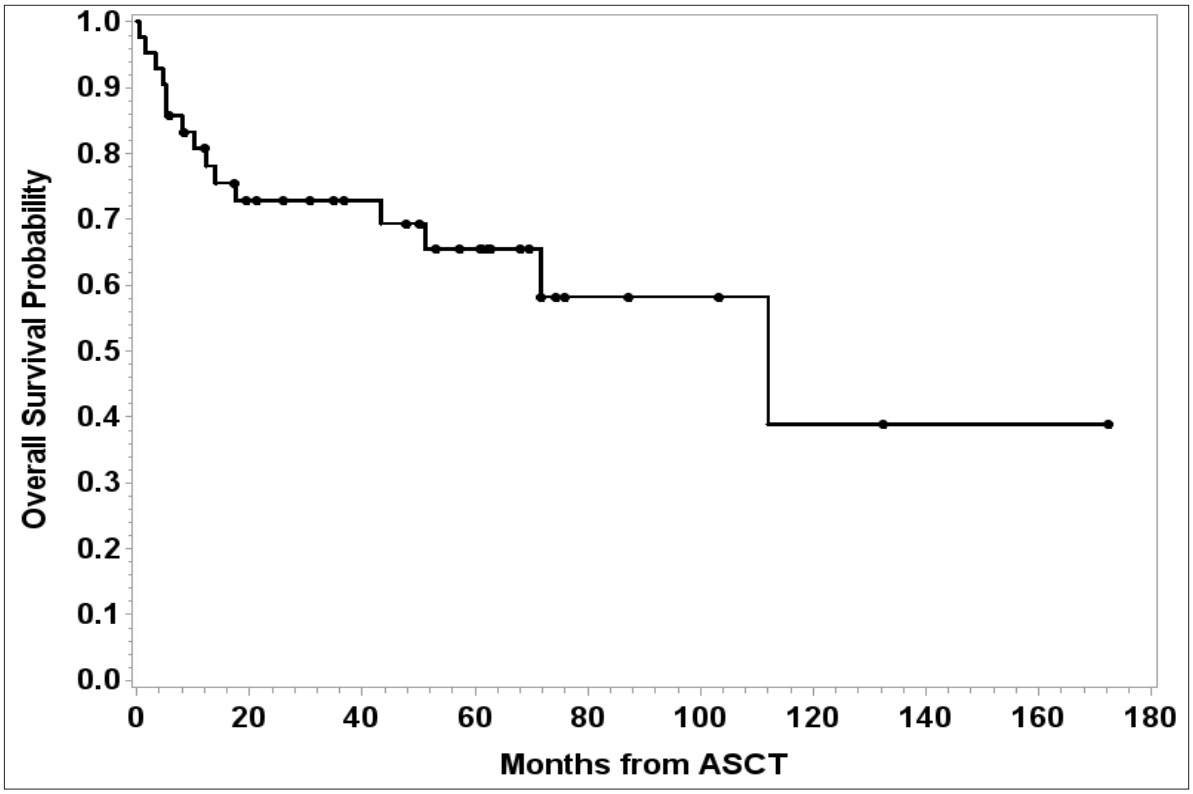

Figure 2. *Overall survival from date of aHSCT*

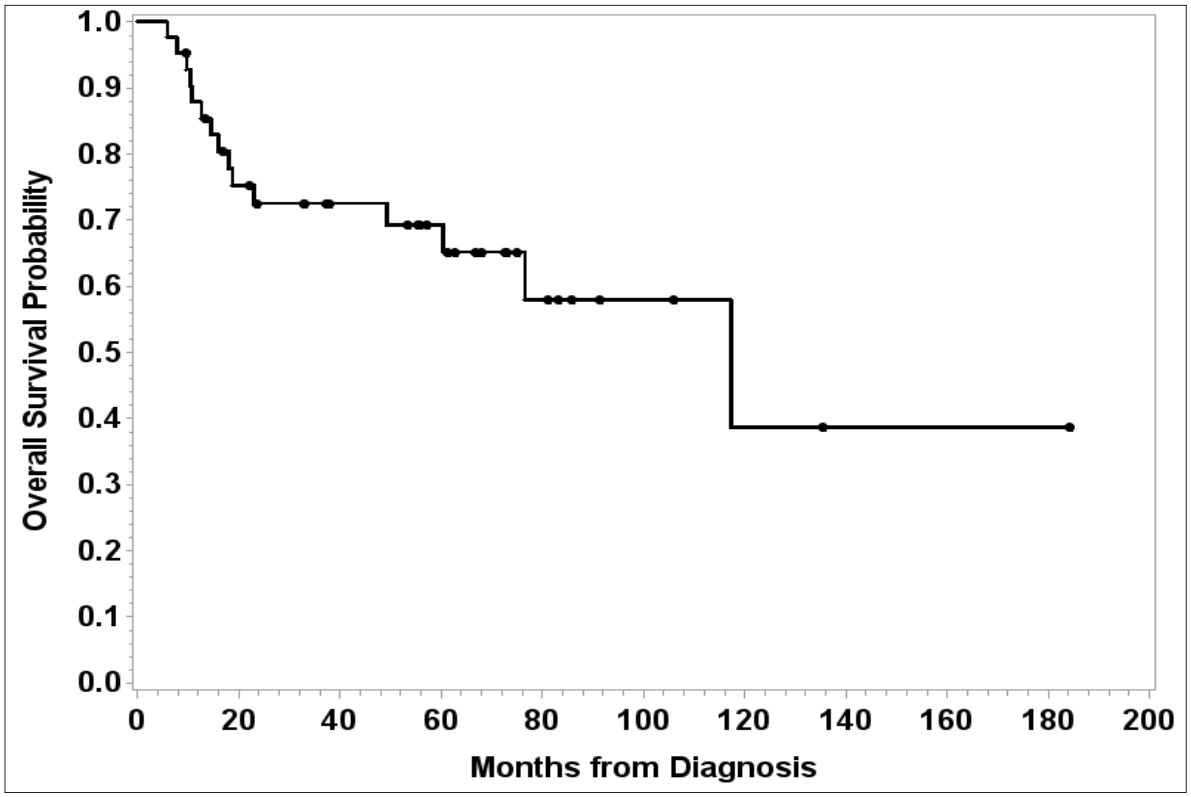

Figure 3. *Overall Survival from date of diagnosis of AL Amyloidosis*

Discussion

Primary systemic amyloidosis or light-chain (AL) amyloidosis is a rare plasma cell dyscrasia with an incidence of 3000-4000 people per year. Untreated patients have median survival of 10-14 months following initial diagnosis. The multi-organ and progressive nature of the disease forges a highly-morbid clinical course and renders its patient population quite fragile in the face of aggressive therapy options. As recently as 15 years ago, the mainstay of therapy involved clinical trials of melphalan and supportive care. Historically, therapy options for treatment of AL had exploited successes of various chemotherapeutic regimens used for the management of multiple myeloma. Despite recent progress through increasing investigations regarding the optimal management of AL, there remains no standard of care regimen for these patients. Since entering the discussion as a viable management option for AL amyloidosis, aHSCT has received more attention in order to ascertain safety and efficacy of pursuing this treatment option (13, 18).

Several retrospective analyses have shown that aHSCT can afford patients a significant clinical response with improved quality of life (9, 12, 13, 15, 18). Concerns regarding pursuing aHSCT have centered predominantly on high transplant-related mortality (19). The only randomized control study that investigated aHSCT versus conventional chemotherapy showed the superiority of melphalan/dexamethasone over melphalan/aHSCT in terms of overall survival due to the high TRM of 24% associated with the aHSCT arm (14). Our experience, though a single-center study, showed a much lower TRM (100 day TRM 4.2%; 1 year TRM 7.2%) as well as impressive PFS (median 106.6 mos.) and OS (median 112.0 mos.), a result that compares favorably to more recent published data with 3 mos. improved TRM of 4 to 9% (9, 10, 15). Our data also showed much improved median PFS and OS that surpasses that in multiple myeloma with median OS of 112 months from aHSCT and 117.2 months from diagnosis, a median PFS of 106.6 mos. from aHSCT as compared to 59.5 and 47 months respectively in multiple Myeloma (15, 20).

These data are encouraging and suggest that autologous aHSCT is a reasonable option for the treatment of AL amyloidosis. Given the extensive systemic involvement of this patient population, it is important to elucidate selection criteria that determine eligibility for high-dose melphalan and aHSCT that improves patient outcomes while reducing TRM. Our data are highly encouraging that aHSCT can emerge as a first line therapy that is safe and efficacious for the treatment of AL amyloidosis.

References

[1] Comenzo RL. How I treat amyloidosis. Blood. 2009;114(15):3147-57.

[2] Merlini G, Seldin DC, Gertz MA. Amyloidosis: Pathogenesis and New Therapeutic Options. J Clin Oncol. 2011.

[3] Desport E, Bridoux F, Sirac C, Delbes S, Bender S, Fernandez B, et al. Al amyloidosis. Orphanet J Rare Dis. 2012;7:54.

[4] Venner CP, Lane T, Foard D, Rannigan L, Gibbs SD, Pinney JH, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood. 2012;119(19):4387-90.

[5] Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012; 119(19):4391-4.

[6] Dispenzieri A, Lacy MQ, Zeldenrust SR, Hayman SR, Kumar SK, Geyer SM, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood. 2007;109(2):465-70.

[7] Sanchorawala V, Finn KT, Fennessey S, Shelton A, Doros G, Zeldis JB, et al. Durable hematologic complete responses can be achieved with lenalidomide in AL amyloidosis. Blood. 2010; 116(11):1990-1.

[8] Reece DE, Hegenbart U, Sanchorawala V, Merlini G, Palladini G, Blade J, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood. 2011;118(4):865-73.

[9] Cibeira MT, Sanchorawala V, Seldin DC, Quillen K, Berk JL, Dember LM, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood. 2011;118(16):4346-52.

[10] Tsai SB, Seldin DC, Quillen K, Berk JL, Ruberg FL, Meier-Ewert H, et al. High-dose melphalan and stem cell transplantation for patients with AL amyloidosis: trends in treatment-related mortality over the past 17 years at a single referral center. Blood. 2012;120(22):4445-6.

[11] Cordes S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Dingli D, et al. Ten-year survival after autologous stem cell transplantation for immunoglobulin light chain amyloidosis. Cancer. 2012;118(24):6105-9.

[12] Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood. 2007;110(10):3561-3.

[13] Dispenzieri A, Kyle RA, Lacy MQ, Therneau TM, Larson DR, Plevak MF, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. Blood. 2004; 103(10): 3960-3.

[14] Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. 2007; 357 (11): 1083-93.

[15] Dispenzieri A, Seenithamby K, Lacy MQ, Kumar SK, Buadi FK, Hayman SR, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. Bone Marrow Transplant. 2013;48(10):1302-7.

[16] Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, 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):4541-9.

[17] Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol. 2005;79(4):319-28.

[18] Comenzo RL, Vosburgh E, Falk RH, Sanchorawala V, Reisinger J, Dubrey S, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. Blood. 1998;91(10):3662-70.

[19] Sher T, Hayman SR, Gertz MA. Treatment of primary systemic amyloidosis (AL): role of intensive and standard therapy. Clin Adv Hematol Oncol. 2012;10(10):644-51.

[20] McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-81.

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