Published in final edited form as:

Heart Vessels. 2014 November ; 29(6): 793–800. doi:10.1007/s00380-013-0419-x.

Clinical and Imaging Predictors of 1-year and Long-Term Mortality in Light Chain (AL) Amyloidosis: A 5-Year Follow Up Study

Raymond Q. Migrino, MD^{1,2,3}, Leanne Harmann, BA, RDCS¹, Richard Christenson, MD¹, and Parameswaran Hari, MD¹

¹Medical College of Wisconsin, Milwaukee WI

²Phoenix Veterans Affairs Health Care System, Phoenix AZ

³University of Arizona, Phoenix AZ, USA

Abstract

Light chain amyloidosis (AL) involves multiorgan failure induced by amyloidogenic light chain proteins and is associated with high mortality. We aim to identify clinical, laboratory and imaging parameters that would predict 1-year and long-term AL mortality. 44 biopsy-proven AL patients (61.5±12 years, 20 females) underwent clinical evaluation including laboratory assays, echocardiography and contrast cardiac magnetic resonance imaging (CMR, n=31) prior to chemotherapy. Patients were prospectively followed for median duration of 62.7 months (IQR 35.5 months). Clinical and laboratory parameters were compared between 1-year survivors versus non-survivors. Univariate Kaplan-Meier survival plots were calculated followed by stepwise logistic regression analysis to assess independent predictors of long-term survival. Eighteen (40.9%) patients died within 1 year and an additional 10 subjects died during long-term follow up. Patients who expired within 1 year presented with more advanced heart failure class, higher alkaline phosphatase and uric acid, lower limb lead voltage on electrocardiography, shorter left ventricular ejection time (ET) on echocardiography and had higher proportion of late gadolinium enhancement (LGE) on CMR. On multivariable analysis, only ET ≥240 ms on echocardiography (HR 5.07, 95% CI 1.83–14.1, p=0.002) and NYHA functional class II–IV presentation (HR 1.0058, 95% CI 1.0014–1.0103, p=0.01) were independent predictors of AL mortality. In conclusion, AL amyloidosis is associated with high 1-year and long-term mortality. Among clinical, laboratory and imaging parameters tested, echocardiographic finding of ET ≥240 ms has independent and additive prognostic value to clinical heart failure evaluation in determining long-term survival of AL patients. This may be important in early identification of at-risk patients.

Keywords

amyloid; heart failure; echocardiography; cardiac magnetic resonance

Introduction

Light chain amyloidosis (AL) involves cardiac and multiorgan dysfunction induced by circulating and deposited amyloidogenic immunoglobulin light chain proteins produced by a clonal population of plasma cells [1, 2]. It is associated with increased morbidity and mortality with cardiac involvement leading to cardiac decompensation being the most important cause of death. Identifying clinical, laboratory and imaging parameters associated with early and long-term mortality may be important in risk-stratification. Prior reports by our group and others showed the prognostic utility of echocardiography, specifically left ventricular ejection time (ET) [3, 4] in predicting AL mortality while evidence of the independent prognostic value of late gadolinium enhancement (LGE) from cardiac magnetic resonance imaging (CMR) on AL mortality has been variable [5–8]. Despite publication of these earlier reports, the comparative roles of ET and LGE *versus each other* as well as other clinical, laboratory and electrocardiographic parameters as predictors of *long-term* (5-year) AL mortality have not been studied. We are testing the hypothesis that ET and LGE are independent predictors of long-term AL mortality and have additive prognostic value to clinically determined heart failure (HF) presentation.

Methods

Patient Population

Between May 2005 and October 2009, 44 consecutive patients with biopsy-proven diagnosis of AL amyloidosis and elevated kappa or lambda immunoglobulin light chains on urine or serum seen at the Medical College of Wisconsin were prospectively included in the study. The study was approved by the local institutional review board. Thirty nine subjects provided informed consent to be part of the longitudinal study of AL. Five subjects with suspected AL awaiting tissue confirmation of diagnosis to qualify for study enrollment died before recruitment to the study, and waiver of consent authorization was obtained from the institutional review board for data collection. All 5 subjects were subsequently found to have biopsy evidence of amyloidosis and elevated light chains on serum or urine. They were included in the analysis to fully capture all consecutive patients with AL amyloidosis seen at the institution. The survival status was verified from hospital or outpatient records; Social Security Death Index was also used for verification until September 2009.

Clinical and Laboratory Evaluation

Presenting New York Heart Association (NYHA) HF class (I–IV) was assessed after enrollment and adjudicated by a cardiologist on the basis of presenting symptoms and signs according to well-established clinical standards [9]. Data on age, gender, systolic blood pressure, heart rate and laboratory values of creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, troponin and brain natriuretic peptide were obtained. Standard 12-lead electrocardiography (ECG) was performed. Low voltage ECG was defined as voltage of ≤ 5 mV in all limb leads [10].

Echocardiography and Cardiac Magnetic Resonance Imaging

The details of the methods have been previously published for echocardiography [4] and CMR [7]. In brief, routine clinical echocardiography was performed using the General Electric Vivid 7 (Waukesha WI) or Philips IE 33, 7500 or 5500 (Philips Medical, Bothell WA). Our previous publication [4] showed the prognostic significance of left ventricular ejection time and we again included this measurement in our multivariable modeling. ET was measured as the duration of flow using standard pulsed-wave Doppler with sample volume located in the left ventricular outflow tract just below the aortic valve leaflets. Left ventricular ejection fraction was obtained using the area length method from the 4-chamber view [11]. Out of the 44 AL subjects, 31 underwent CMR studies. Standard CMR methods were performed for LGE imaging. A General Electric 1.5 Tesla CV scanner with 8-channel cardiac coil were used. 0.1 mmol/kg of gadolinium (gadodiamide, GE Healthcare or gadobenate dimeglumine, Bracco Diagnostics) was injected followed by imaging after ~5 minute delay in short axis and multiple long axis views. Gated segmented inversion-recovery prepared gradient echo pulse sequence with field of view of 38–42 cm, matrix of 256x192–256, slice thickness of 7–8 mm and interslice gap of 2–3 mm, inversion time adjusted to null normal myocardium (~175–300 ms), 1–2 excitations and 2 R-R intervals. The details of the determination of the optimal inversion time has been previously reported [7]. Two expert CMR readers (RQM and RC) independently adjudicated the presence or absence of LGE with agreement of the findings in all cases.

Data and Statistical Analyses

Data are expressed as mean±standard deviation. Continuous variables were compared between groups using Student t test or Mann-Whitney rank sum test for normal or non-normal distribution data, respectively. Categorical variables were compared using the chi-square test or Fisher exact test (in cases where a category bin n = 5). Significant p value was set at p<0.05. Stratified estimates of survival probabilities were computed using Kaplan-Meier estimators [12] and log-rank test was used to test for group differences in survival curves from all-cause mortality (MedCalc 9.6.4.0, Mariakerke, Belgium). The cutoff values for ET and alkaline phosphatase used for dichotomy were derived from receiver operating characteristic curve analysis to determine the sensitivity and specificity in predicting 1-year mortality among patients who were censored or alive after 1-year follow up. Variables associated with 1-year mortality were entered into a Cox stepwise multivariable analysis (variable removed if p>0.1 and entered if p<0.05) to derive the final model for prediction of all-cause mortality (MedCalc 9.6.4.0, Mariakerke, Belgium). No data imputation was performed.

Results

Within 1 year of study inclusion, 18 of 44 patients died (40.9%) and during long-term follow up, an additional 10 patients expired. The most common cause of mortality involved multiorgan failure (Table 1). Direct cardiac contribution to the cause of death was found in 14/25 (56%) of deaths with known causes.

Patients who expired within 1 year of study inclusion had significantly more advanced heart failure class, higher alkaline phosphatase levels, lower limb lead voltages on ECG, had a higher proportion of presence of LGE on CMR and had shorter left ventricular ejection time on echocardiography (Table 2). The proportion receiving autologous stem cell transplantation is also less in non-survivors compared to survivors (Table 2). Thirty eight patients (86%) received chemotherapy and melphalan was the most commonly used chemotherapeutic agent (Table 3).

Receiving operator characteristic (ROC) curve analyses showed that alkaline phosphatase level of 85 IU/L (AUC 0.73, $p=0.004$) and ET of 240 ms (AUC 0.68, $p<0.04$) had the best ability to discriminate between 1-year survivors and non-survivors.

On univariate analysis, heart failure class II–IV, LVET ≥ 240 ms, alkaline phosphatase ≥ 85 IU/L, non-utilization of autologous stem cell transplantation, presence of low voltage on ECG and LGE on CMR, but not serum uric acid, were associated with poor long-term survival (Figure 1). Following logistic regression analysis wherein each of these variables were put in the model using a stepwise analysis, only LVET ≥ 240 ms (HR 5.07, 95% CI 1.83–14.1, $p=0.002$) and HF class II–IV (HR 1.0058, 95% CI 1.0014–1.0103, $p=0.01$) were found to be independent predictors of long term AL mortality (overall model fit chi-square 15.7, $p=0.0004$).

Kaplan Meier analysis was performed to assess survival of subjects stratified as to whether they have HF (Class II–IV), LVET ≥ 240 ms, both or neither (Figure 2). Subjects who have both have the worst prognosis while subjects with neither had the best survival.

Discussion

We report the novel observation that on long-term (median >5 years) follow up, left ventricular ejection time using echocardiography is an important independent predictor of long-term AL mortality and has additive prognostic value to heart failure class presentation. Our results show that in addition to ET and HF classification, presence of late gadolinium enhancement, low voltage on ECG and increased alkaline phosphatase are associated with increased 1-year mortality while eligibility for and treatment with autologous stem cell transplant with chemotherapy is associated with reduced 1-year mortality. These findings may be important in early risk stratification of AL subjects. Importantly, despite use of chemotherapy in 88.6% of patients, 1-year mortality was 40.9% and 63.6% of AL patients expired during the study follow up duration.

Although amyloidogenic light chain proteins are deposited in multiple organs such as the liver, gastrointestinal tract, kidneys and peripheral nerves, the major cause of morbidity and mortality in AL involve cardiac complications, notably heart failure and arrhythmias/sudden cardiac death [1, 2]. There is increasing clinical [13–16] and preclinical evidence [17–19] that the major toxic species in AL is the soluble prefibrillar species. This is supported by disease stabilization following eradication of clonal plasma cells producing light chain proteins through chemotherapy±autologous stem cell transplantation, currently the only treatment available for the disease, despite persistence of amyloid deposits [13, 15]. Toxicity

to the cardiovascular system involves amyloid deposition in the cardiac interstitium leading to cardiomyocyte toxicity [17–19], as well as oxidative stress and apoptotic injury to the microvessels and endothelial cells [20–22]. Because of the critical role of cardiac involvement in disease course, clinical, laboratory and imaging studies that define presence and extent of cardiac involvement are important in disease management. Evidence of cardiac involvement includes diffuse low voltage on ECG, elevation of cardiac biomarkers such as troponins, brain natriuretic peptides (BNP) and N-terminal pro-BNP and thickening of the left ventricle on echocardiography or CMR despite absence of hypertrophy on ECG. The presence of late gadolinium enhancement on CMR with distinct subendocardial or diffuse myocardial distribution as well as unusual gadolinium kinetics that reflect myocardial levels close to blood pool levels has recently been available as a clinical tool to noninvasively establish cardiac involvement, reducing the need for invasive endomyocardial biopsy [1, 2, 5–8, 23].

The medium-term prognostic value of CMR or echocardiography for predicting AL mortality have separately been reported by our group and others. Late gadolinium enhancement on CMR was found to be associated with poor survival even after adjustment for heart failure class (median follow up 29 months) in the same cohort of patients [7] but other investigators found that LGE presence did not add prognostic value to heart failure class in predicting AL mortality at median follow up durations of 29 months [8], 21 months [5] and >32 months [6]. Maceira and colleagues, however, reported that the difference in gadolinium distribution between subepicardial and subendocardial myocardial regions assessed by T1 signal, and not the gross presence of LGE, is predictive of AL mortality [5]. In separate reports not involving CMR imaging, we and others reported that left ventricular ejection time on echocardiography is a strong independent predictor of AL mortality at median follow up durations of 29 months [4] and 18 months [3]. As far as we are aware, our findings are the first to compare the 5-year independent prognostic value of the two most commonly used imaging techniques to assess cardiac involvement in AL, CMR and echocardiography, versus other clinical and laboratory parameters. The findings enhance the justification for the use of these diagnostic imaging modalities to assess 1-year and long-term risk of AL subjects.

The finding that LGE is not an independent predictor of long-term AL mortality is consistent with the observations of other investigators [5, 6, 8], although 1-year mortality was higher in patients with LGE on CMR versus those without. This likely reflects the collinearity between LGE presence and extent of heart failure class presentation. The basis for the long-term prognostic value of ET remains undetermined. Left ventricular ejection time is an old, established measure of left ventricular performance that has been used to assess valvular, coronary artery, pericardial, hypertensive and amyloid diseases [24–28]. In AL, short ET may reflect the inability of the infiltrated myocardium to increase end-diastolic volumes, prolongation of preejection period due to myocardial dysfunction and abnormal ventriculoatrial coupling [4, 27–29]. Further mechanistic studies need to be performed to establish the pathophysiologic basis of why short ET is strongly associated with AL mortality independent of heart failure class presentation. On the other hand, ET is easily measured from well-established routine echocardiography clinical protocols and should be routinely measured and reported in AL patients to enhance patient risk-stratification.

Clinically, autologous stem cell transplantation allows for utilization of more intensive chemotherapy regimen to eradicate clonal plasma cells producing amyloidogenic light chain proteins, but it is associated with increased mortality in patients with advanced heart failure[30]. Therefore oncologists utilize a risk-adapted approach to determine eligibility for stem cell transplantation which makes patients with advanced cardiac involvement ineligible for the procedure [30, 31]. It is therefore not surprising that when stem cell transplantation is put in the model with HF class, it fell off as an independent predictor because of the colinearity between HF class and eligibility for receiving stem cell transplantation. In light of the prognostic value of ET in AL, the addition of ET in the risk-adapted approach to determine eligibility for stem cell transplantation needs to be further studied. Furthermore, utilization of imaging and clinical parameters found to be useful in detecting cardiac involvement and predicting short and long term risk could enhance current practice of comprehensive patient assessment that might impact the overall adverse outcomes of these patients.

It is important to point out that the current study is an extension and expansion of our previously published work on the prognostic use of echocardiography [4] and CMR [7]. Although derived from the same cohort of subjects as the previous studies, the important novel observations of the current study are validating the independent prognostic value on 5-year follow up and comparing for the first time using multivariable modeling the prognostic value of relevant echocardiographic and CMR parameters versus each other and clinical parameters, that might be helpful to providers in making clinical decisions.

Study Limitations

The study has several important limitations. The sample size involved in the study is small although the number of mortality events during follow up (28 out of 44 patients) resulting from this often-fatal disease somewhat mitigates this limitation as far as data analysis is concerned. The findings need to be validated by other long-term studies involving a larger population size. We did not have data on differential T1 signal on CMR LGE between epicardium and endocardium [5], echocardiographic myocardial strain [3] and NT-proBNP [32] that have previously been reported to have independent prognostic value in AL, and therefore their relative value to ET and HF class remain unknown. In addition, we did not have imaging data on T2-weighted myocardial characteristics, which other investigators showed to have potential prognostic value in cardiac amyloidosis [33] and other types of cardiomyopathy [34].

Conclusions

AL remains a highly lethal disease despite utilization of chemotherapy with or without use of autologous stem cell transplantation. Identification of clinical, laboratory and imaging predictors of short-term and long-term survival is important in patient risk-stratification. Short left ventricular ejection time on echocardiography (< 240 ms) is an independent prognostic marker of short term and long term AL mortality in addition to heart failure class presentation.

Acknowledgments

The authors (RQM, PH) received amyloidosis research support from the Amyloidosis Foundation, VA Merit Grant, Carl T. Hayden Medical Research Foundation, NIH R21, American Heart Association Grant In Aid, American Cancer Society and Greater Milwaukee Foundation. The study was supported by Veterans Affairs employment. The contents do not represent the views of the Veterans Affairs or the United States government.

References

1. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: a review. *J Am Heart Assoc.* 2012; 1(2):e000364. [PubMed: 23130126]
2. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation.* 2005; 112(13):2047–60. [PubMed: 16186440]
3. Bellavia D, Pellikka PA, Al-Zahrani G, Abraham TP, Dispenzieri A, Miyazaki C, Lacy MQ, Scott CG, Oh JK, Miller FA. Independent predictors of survival in primary (AL) amyloidosis, including cardiac biomarkers and left ventricular strain imaging: an observational cohort study. *J Am Soc Echocardiogr.* 2010; 23(6):643–652. [PubMed: 20434879]
4. Migrino RQ, Maredu RK, Eastwood D, Bowers M, Harmann L, Hari P. Left ventricular ejection time on echocardiography predicts long-term mortality in light chain amyloidosis. *J Am Soc Echocardiogr.* 2009; 22(12):1396–1402. [PubMed: 19880277]
5. Maceira AM, Prasad SK, Hawkins PN, Roughton M, Pennell DJ. Cardiovascular magnetic resonance and prognosis in cardiac amyloidosis. *J Cardiovasc Magn Reson.* 2008; 10(1):54. [PubMed: 19032744]
6. Mekinian A, Lions C, Leleu X, Duhamel A, Lamblin N, Coiteux V, De Groote P, Hatron PY, Facon T, Beregi JP, Hachulla E, Launay D. Prognosis assessment of cardiac involvement in systemic AL amyloidosis by magnetic resonance imaging. *Am J Med.* 2010; 123(9):864–868. [PubMed: 20800158]
7. Migrino RQ, Christenson R, Szabo A, Bright M, Truran S, Hari P. Prognostic implication of late gadolinium enhancement on cardiac MRI in light chain (AL) amyloidosis on long term follow up. *BMC Med Phys.* 2009; 9:5. [PubMed: 19416541]
8. Ruberg FL, Appelbaum E, Davidoff R, Ozonoff A, Kissinger KV, Harrigan C, Skinner M, Manning WJ. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. *Am J Cardiol.* 2009; 103(4):544–549. [PubMed: 19195518]
9. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels. Boston: Little Brown; 1964.
10. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. *Am J Cardiol.* 2005; 95(4):535–537. [PubMed: 15695149]
11. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986; 57(6):450–458.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958; 53:457–481.
13. Dubrey S, Mendes L, Skinner M, Falk RH. Resolution of heart failure in patients with AL amyloidosis. *Ann Intern Med.* 1996; 125(6):481–484. [PubMed: 8779461]
14. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, Falk RH. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. *QJM.* 1998; 91(2):141–157. [PubMed: 9578896]
15. Kyle RA, Wagoner RD, Holley KE. Primary systemic amyloidosis: resolution of the nephrotic syndrome with melphalan and prednisone. *Arch Intern Med.* 1982; 142(8):1445–1447. [PubMed: 7103624]
16. Palladini G, Lavatelli F, Russo P, Perlini S, Perfetti V, Bosoni T, Obici L, Bradwell AR, D'Eril GM, Fogari R, Moratti R, Merlini G. Circulating amyloidogenic free light chains and serum N-

- terminal natriuretic peptide type B decrease simultaneously in association with improvement of survival in AL. *Blood*. 2006; 107(10):3854–3858. [PubMed: 16434487]
17. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, Apstein CS, Liao R. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. *Circ Res*. 2004; 94(8):1008–1010. [PubMed: 15044325]
 18. Liao R, Jain M, Teller P, Connors LH, Ngoy S, Skinner M, Falk RH, Apstein CS. Infusion of light chains from patients with cardiac amyloidosis causes diastolic dysfunction in isolated mouse hearts. *Circulation*. 2001; 104(14):1594–1597. [PubMed: 11581134]
 19. Shi J, Guan J, Jiang B, Brenner DA, Del Monte F, Ward JE, Connors LH, Sawyer DB, Semigran MJ, Macgillivray TE, Seldin DC, Falk R, Liao R. Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38alpha MAPK pathway. *Proc Natl Acad Sci U S A*. 2010; 107(9):4188–4193. [PubMed: 20150510]
 20. Franco DA, Truran S, Burciu C, Gutterman DD, Maltagliati A, Weissig V, Hari P, Migrino RQ. Protective role of clusterin in preserving endothelial function in AL amyloidosis. *Atherosclerosis*. 2012; 225(1):220–223. [PubMed: 22981431]
 21. Migrino RQ, Hari P, Gutterman DD, Bright M, Truran S, Schlundt B, Phillips SA. Systemic and microvascular oxidative stress induced by light chain amyloidosis. *Int J Cardiol*. 2010; 145(1):67–68. [PubMed: 19446898]
 22. Migrino RQ, Truran S, Gutterman DD, Franco DA, Bright M, Schlundt B, Timmons M, Motta A, Phillips SA, Hari P. Human microvascular dysfunction and apoptotic injury induced by AL amyloidosis light chain proteins. *Am J Physiol Heart Circ Physiol*. 2011; 301(6):H2305–H2312. [PubMed: 21963839]
 23. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, Sheppard MN, Poole-Wilson PA, Hawkins PN, Pennell DJ. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation*. 2005; 111(2):186–193. [PubMed: 15630027]
 24. Chan GS, Middleton PM, Celler BG, Wang L, Lovell NH. Automatic detection of left ventricular ejection time from a finger photoplethysmographic pulse oximetry waveform: comparison with Doppler aortic measurement. *Physiol Meas*. 2007; 28(4):439–452. [PubMed: 17395998]
 25. Lewis RP. Diagnostic value of systolic time intervals in man. *Cardiovasc Clin*. 1975; 6(3):245–264. [PubMed: 1100237]
 26. Lewis RP, Rittogers SE, Froester WF, Boudoulas H. A critical review of the systolic time intervals. *Circulation*. 1977; 56(2):146–158. [PubMed: 872305]
 27. Tei C, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. *J Am Coll Cardiol*. 1996; 28(3):658–664. [PubMed: 8772753]
 28. Wizenberg TA, Muz J, Sohn YH, Samlowski W, Weissler AM. Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the noninvasive diagnosis of cardiac amyloidosis. *Am Heart J*. 1982; 103(4 Pt 1):468–473. [PubMed: 6278906]
 29. Cheng HM, Yu WC, Sung SH, Wang KL, Chuang SY, Chen CH. Usefulness of systolic time intervals in the identification of abnormal ventriculo-arterial coupling in stable heart failure patients. *Eur J Heart Fail*. 2008; 10(12):1192–1200. [PubMed: 19004668]
 30. Jantunen E, Itala M, Lehtinen T, Kuittinen O, Koivunen E, Leppa S, Juvonen E, Koistinen P, Wilund T, Nousiainen T, Remes K, Volin L. Early treatment-related mortality in adult autologous stem cell transplant recipients: a nation-wide survey of 1482 transplanted patients. *Eur J Haematol*. 2006; 76(3):245–250. [PubMed: 16412136]
 31. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar S. Transplantation for amyloidosis. *Curr Opin Oncol*. 2007; 19(2):136–141. [PubMed: 17272986]
 32. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, McConnell JP, Litzow MR, Gastineau DA, Tefferi A, Inwards DJ, Micallef IN, Ansell SM, Porrata LF, Elliott MA, Hogan WJ, Rajkumar SV, Fonseca R, Greipp PR, Witzig TE, Lust JA, Zeldenrust SR, Snow DS, Hayman SR, McGregor CG, Jaffe AS. Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. *Blood*. 2004; 104(6):1881–1887. [PubMed: 15044258]

33. Wassmuth R, Abdel-Aty H, Bohl S, Schulz-Menger J. Prognostic impact of T2-weighted CMR imaging for cardiac amyloidosis. *Eur Radiol.* 2011; 21(8):1643–1650. [PubMed: 21720941]
34. Hen Y, Iguchi N, Machida H, Takada K, Utanohara Y, Sumiyoshi T. High signal intensity on T2-weighted cardiac magnetic resonance imaging correlates with the ventricular tachyarrhythmia in hypertrophic cardiomyopathy. *Heart Vessels.* 2012;10.1007/s00380-012-0300-3

Figure 1.

Comparisons of long-term survival in AL. On univariate Kaplan-Meier analysis, heart failure class II–IV (A), LVET ≥ 240 ms (B), alkaline phosphatase ≥ 85 IU/L (C), non-utilization of autologous stem cell transplantation (D), presence of low limb lead voltage on ECG (E) and presence of LGE on CMR (F) were all associated with increased long term AL mortality.

Figure 2.

Survival by HF class and ET. Subjects were grouped into the following: 0 (HF class I and ET>240 ms, ET $\leq$ 240 (ET $\leq$ 240 and HF class I), HF II–IV (HF class II–IV and ET>240 ms) and ET $\leq$ 240 and HF II–IV. Subjects without HF and with ET>240 ms had best survival while subject with both HF and ET $\leq$ 240 had the worst survival ($p=0.0004$).

Table 1

Causes of mortality

Cause of mortality	Number
Multiorgan failure	10
Intractable heart failure, EMD, ventricular arrhythmia or sudden cardiac death	8
Renal failure	3
Refractory multiple myeloma	2
Sepsis	1
Respiratory failure	1
Unknown	3
Total	28

Table 2

Clinical, laboratory and imaging characteristics.

Variable	All Patients	1-year Survivors	1-Year Non-survivors	p-value
Age (years)	61.5 (SD12)	62.3 (SD12)	60.4 (SD12)	0.62
Females (%)	45	54	33	0.30
Heart rate (bpm)	80.4 (SD20)	79.0 (SD22)	82.4 (SD16)	0.59
Systolic blood pressure (mmHg)	122 (SD22)	125 (SD26)	118 (SD16)	0.31
LVEF (%)	64.8 (SD16)	66.5 (SD14)	62.3 (SD18)	0.43
Chemotherapy (%)	86.4	84.6	94.4	0.63
Chemotherapy+SCT	34.9	52	11.1	0.009
Heart Failure Class (%)				0.0038
I (n=19)	43.2	89.5	10.5	
II (n=14)	31.8	42.8	57.1	
III (n=4)	9.1	25.0	75.0	
IV (n=7)	15.9	28.6	71.4	
Troponin (ng/mL)	0.69 (SD1.8)	0.74 (SD2.3)	0.62 (SD0.66)	0.85
Brain natriuretic peptide (pg/mL)	1063 (SD1300)	736 (SD1301)	1390 (SD1268)	0.22
Creatinine (mg/dL)	1.56 (SD1.1)	1.38 (SD0.9)	1.84 (SD1.3)	0.18
Alkaline phosphatase (IU/L)	118.2 (SD117)	88.0 (SD41)	166.3 (SD173)	0.038
AST (U/L)	39.3 (SD69)	25.2 (SD10)	63.4 (SD107)	0.10
ALT (U/L)	37.8 (SD63)	27.0 (SD17)	59.4 (SD102)	0.15
Uric acid (mg/dL)	7.15 (SD0.4)	6.2 (SD2.2)	8.4 (SD3.1)	0.01
ECG Low Voltage (%)	43	19	58	0.02
ECG voltage (I, aVF)	4.5 (SD2.1)	5.3 (SD2)	3.6 (SD1.5)	0.007
LGE positive (%)	77	65	100	0.03
LVET (ms)	267 (SD43)	280 (SD41)	250 (SD42)	0.03

Table 3

Chemotherapeutic agents used

Chemotherapy regimen	Number of subjects
melphalan	13
melphalan, dexamethasone/prednisone	7
bortezomib, cyclophosphamide, dexamethasone/prednisone	3
bortezomib	2
bortezomib, dexamethasone, melphalan	2
melphalan, dexamethasone, thalidomide/lenalidomide	1
thalidomide, dexamethasone	1
bortezomib, melphalan	1
cyclophosphamide, thalidomide	1
cyclophosphamide	1
bortezomib, thalidomide, dexamethasone	1
cyclophosphamide, dexamethasone	1
bortezomib, cyclophosphamide, dexamethasone, lenalidomide	1
bortezomib, dexamethasone	1
cyclophosphamide, dexamethasone, rituximab	1
bortezomib, cyclophosphamide	1
none	6