bjh research paper

A longitudinal evaluation of health-related quality of life in patients with AL amyloidosis: associations with health outcomes over time

Vaishali Sanchorawala,[1] Kristen L. McCausland,[2] Michelle K. White,[2] Martha S. Bayliss,[2] Spencer D. Guthrie,[3] Stephen Lo[1] and Martha Skinner[1]

[1]Amyloidosis Center, Boston University School of Medicine, Boston, MA, [2]Optum, Johnston, RI, and [3]Prothena Biosciences, Inc, South San Francisco, CA, USA

Received 18 May 2017; accepted for publication 20 June 2017

Correspondence: Kristen L. McCausland, Optum Inc, 1301 Atwood Avenue, Suite 311N, Johnston, RI 02919, USA.
E-mail: kmccausland@qualitymetric.com

A portion of this work was presented in poster format at the International Society of Amyloidosis 2016 Symposium; July 3–7; Uppsala, Sweden.

Summary

Light chain (AL) amyloidosis is a rare disease associated with significant, irreversible organ dysfunction and high case fatality. An observational study was conducted to assess health-related quality of life (HRQoL) in patients treated for AL amyloidosis between 1994 and 2014 with both high dose melphalan and stem cell transplantation (HDM/SCT) or non-SCT chemotherapy regimens. The SF-36v1® Health Survey (SF-36) was administered to assess HRQoL during clinic visits. Analysis of variance was used to compare pre- and post-treatment HRQoL within each treatment group to an age- and gender-adjusted general population (GP) normative sample. Cox proportional hazard models were fit to examine associations between pre-treatment levels of HRQoL and mortality within 1 and 5 years after initiating specific treatment regimens (HDM/SCT: $n = 402$; non-SCT chemotherapy regimens: $n = 172$). Among patients who received HDM/SCT, there were significant improvements following treatment in vitality, social functioning, role-emotional and mental health. Worse pre-treatment SF-36 physical component scores were associated with a greater risk of mortality in both treatment groups and follow-up periods ($P \leq 0{\cdot}005$ for both). [Correction added on 20 October 2017, after first online publication: This *P* value has been corrected]. Using HRQoL assessments in every physician visit or treatment may provide valuable insights for treating rare conditions like AL amyloidosis.

Keywords: AL amyloidosis, health-related quality of life, SF-36, stem cell transplantation, mortality.

Light-chain (AL) amyloidosis is a plasma cell dyscrasia, characterized by amyloid deposits derived from immunoglobulin light chains in tissues and vital organs (Falk *et al*, 1997). Although rare (i.e., 8–12 cases per million person-years; Kyle *et al*, 1992; Pinney *et al*, 2013), AL amyloidosis is associated with significant, irreversible organ dysfunction and high rates of severe morbidity and mortality in affected individuals (Kyle & Gertz, 1995; Merlini *et al*, 2011). Although the disease can impact any organ, the kidney and the heart are the most commonly affected (Falk *et al*, 1997). Kidney and heart involvement can lead to critical complications, such as renal failure, cardiomyopathy, and pericardial and pleural effusions (Merlini *et al*, 2011). Disease severity and prognosis are highly dependent on the extent and types of organ involvement, as well as early diagnosis and treatment (Merlini *et al*, 2011; Palladini *et al*, 2014).

No therapeutic regimen has been approved for the treatment of AL amyloidosis by either the United States Food and Drug Administration or the European Medicines Agency to date. Accordingly, clinicians often rely on therapies adapted from effective treatments for multiple myeloma. High dose melphalan and stem cell transplantation (HDM/SCT), proteasome inhibitors and immunomodulatory drugs are commonly used to reduce the production of amyloidogenic light chains produced by clonal plasma cell dyscrasia (Palladini *et al*, 2014; Sanchorawala, 2014). Effective treatments for AL amyloidosis are associated with haematological responses, organ responses and improvements in survival; however, treatment decisions are often complex and tailored to the disease characteristics for a particular patient (Comenzo *et al*, 2012). Furthermore, the risk of treatment-related toxicity may have implications for

First published online 29 August 2017
British Journal of Haematology, 2017, **179,** 461–470
doi: 10.1111/bjh.14889

treatment decisions, adherence and health-related quality of life (HRQoL).

The impact of AL amyloidosis and its treatments on HRQoL has not been studied extensively. Evidence from cross-sectional studies in AL amyloidosis shows broad deficits in functioning and well-being in both treatment-naïve patients and in heterogeneous groups of patients with varied disease severity and treatment history (Seldin *et al*, 2004; Caccialanza *et al*, 2012; Bayliss *et al*, 2017). Only one study has reported on longitudinal assessments of HRQoL and the results indicated that greater pre- and post-treatment HRQoL, as measured by the SF-36® Health Survey (SF-36), is associated with reduced risk of mortality among patients who received HDM/SCT treatments (Seldin *et al*, 2004). Additionally, treatment with HDM/SCT can also lead to improvements in HRQoL in patients with AL amyloidosis (Seldin *et al*, 2004).

Given the functional burden that AL amyloidosis may place on patients, understanding HRQoL is of great value to a variety of stakeholders, including healthcare providers, drug developers, regulatory agencies, payers and, particularly, patients themselves. Patient-centred treatment approaches that monitor HRQoL and symptom burden can foster better communication and treatment decisions between healthcare providers and their patients. By identifying the specific aspects of HRQoL that are in the most need for improvement, stakeholders can also better target the development of future treatments. Furthermore, examining the impact of treatments on HRQoL in both the short- and long-term may help to characterize the overall effectiveness of specific treatment regimens.

The purpose of this study was to longitudinally assess HRQoL in patients with AL amyloidosis. The primary study objective was to examine the association between baseline HRQoL of patients with AL amyloidosis and the risk of 1- and 5-year mortality separately for those who received HDM/SCT or a standard chemotherapy regimen without SCT. As a secondary study objective, we compared the functional burden of AL amyloidosis in patients who received HDM/SCT or a standard chemotherapy without SCT to norms for functional well-being in a general population.

Methods

Sample/study procedures

The present study is a retrospective data analysis of a cohort of patients with AL amyloidosis who were evaluated at the Amyloidosis Center of Boston University School of Medicine and Boston Medical Center (BMC) between 1994 and 2014 ($N = 1822$). Basic demographics, disease characteristics and HRQoL information were documented at an initial evaluation at the centre. Time-varying characteristics were updated at follow-up clinic visits, if appropriate. Although patients were encouraged to provide HRQoL information at each clinic visit, there was no standard schedule for the collection of HRQoL data at specific study time points. Post-treatment follow-up assessments for this study were defined as 18-month follow-up visits. Informed consent for data collection was obtained according to the Declaration of Helsinki.

To meet the objectives of the current study, several analytic samples were created. A flowchart depicting the selection process for each sample is presented in Fig 1. Of the 1822 patients seen at the Amyloidosis Center of Boston University School of Medicine and BMC between 1994 and 2014, 35% were excluded due to incomplete treatment records ($n = 645$). The vast majority of these exclusions (73%) were for patients who only came to the clinic once for an initial consultation and did not continue with treatment and/or follow-up.

First, to conduct analyses that compared pre- and post-treatment burden among patients with AL amyloidosis to HRQoL norms for the general population, we included patients from both treatment groups who had either a pre- and/or a post-treatment observation of SF-36 data. The pre-treatment sample included 402 patients who received HDM/SCT and 172 who received non-SCT chemotherapy regimens. For the post-treatment sample, we included 230 patients who received HDM/SCT and 73 who received a non-SCT chemotherapy regimen. Patients were eligible for the time to event analysis (HDM/SCT: $n = 402$; non-SCT chemotherapy regimens: $n = 172$) if they: (i) were not missing treatment-related data; (ii) received HDM/SCT or non-SCT chemotherapy regimens after their initial evaluation and (iii) completed an SF-36 assessment within 120 days prior to initiating treatment.

Finally, patients were eligible for the change in HRQoL analyses (HDM/SCT: $n = 162$; non-SCT chemotherapy regimens: $n = 31$) if they: (i) met the eligibility requirements for the time to event analysis; and (ii) completed at least one post-treatment SF-36 assessment within 6–18 months following treatment initiation.

Study measures

The following demographic and disease characteristics were used to characterize the sample and were considered as potential confounders in multivariable analyses: *age* (continuous); *gender* (male *versus* female); *race/ethnicity* (non-white *versus* white); *educational attainment* [categorical: <high school diploma, high school diploma or general educational development.; some college, associate's degree, or technical certificate; bachelor's degree (B.A, B.S); graduate degree]; *marital status* (currently married *versus* other); *time since diagnosis* (continuous; number of months from diagnosis to baseline data collection), *type of organ/system involvement* (indicator variables: heart, kidney, liver, nervous system, gastrointestinal and soft tissue), *number of organs involved* (categorical: one/two, three, four or ≥five).

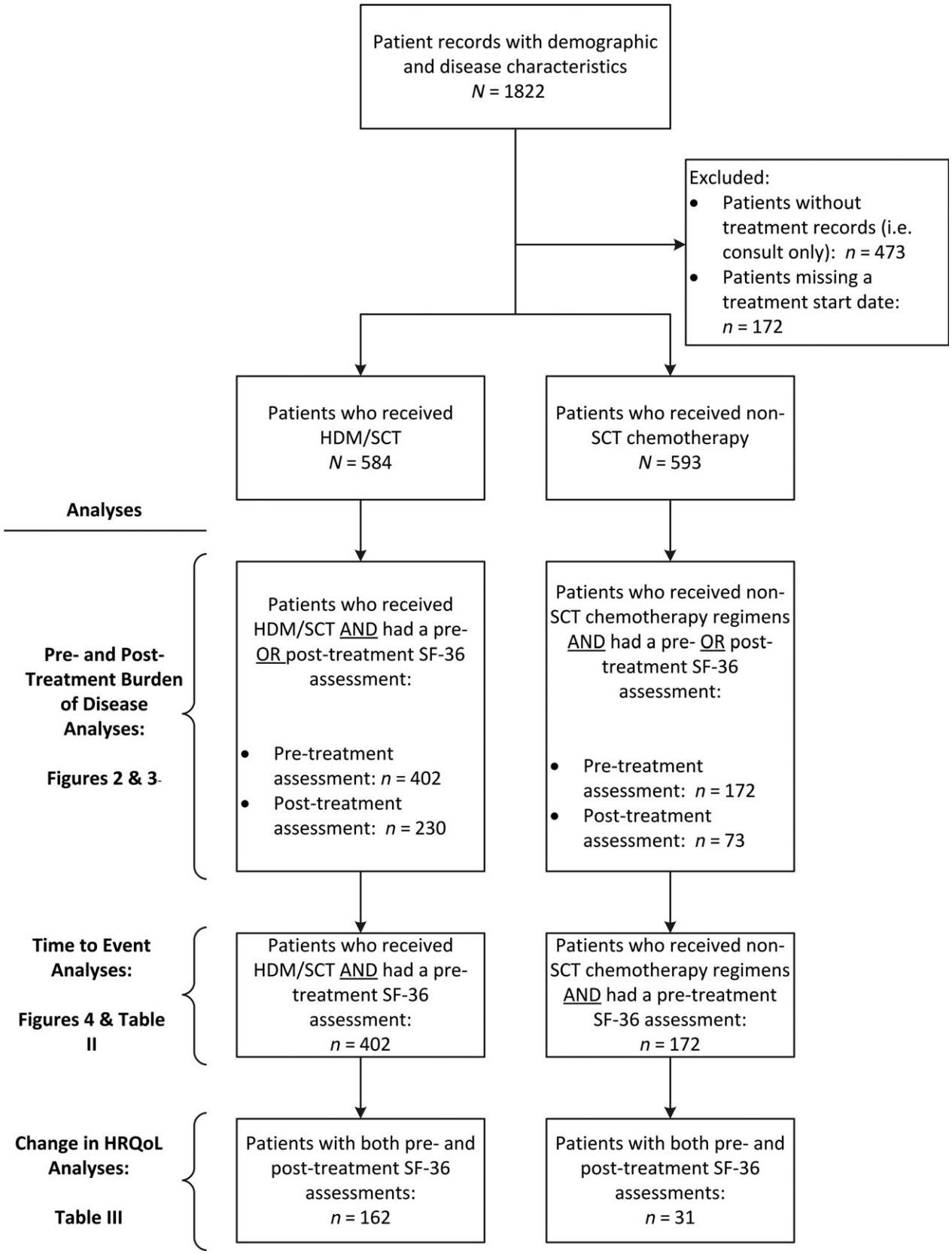

Fig 1. Flowchart for identifying analytic samples. HDM, high dose melphalan; HRQoL, health-related quality of life; SCT, stem cell transplantation. [Correction added on 20 October 2017, after first online publication: some *n* values have been corrected or deleted].

The SF-36v1®, a 36-item generic measure of HRQoL with a standard 4-week recall, was used as the primary measure of HRQoL (Maruish, 2011). Item responses were used to derive scores for the eight scales: physical functioning (PF), role physical (RP; role limitations due to physical problems), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role emotional (RE; role limitations due to emotional problems) and mental health (MH). These eight scales were, in turn, used to calculate two scores that summarize the physical and mental aspects of functioning and well-being [i.e., the physical component summary (PCS) and the mental component summary (MCS), respectively]. All scores relied on a norm-based scoring approach, which standardized the distributions of each scale or summary score to a mean of 50 and a standard deviation of 10 based on data from a nationally representative sample of US adults ($N = 2031$) conducted in 1998 (Ware *et al*, 2000a,b). For all scales and summary measures, higher scores represent more favourable functioning. Previously reported minimal important differences (MIDs) for each of the eight scales, PCS, and MCS were used to identify differences that were clinically meaningful (Maruish, 2011).

The outcome for the primary study objective was all-cause mortality. Deaths were reported by patients' family or physician or confirmed using the Social Security Death Index. Dates and cause of death were recorded in patient records.

Statistical analyses

Patient characteristics were compared by the availability of pre-treatment SF-36 data and by treatment received. Unadjusted differences between the subgroups were examined using chi-square and two sample *t*-tests for categorical and continuous variables, respectively. Wilcoxon–Mann–Whitney tests were used to test for significant differences in SF-36 scores by subgroups that violated the normality assumption.

Pre- and post-treatment assessments were compared to general population norms for each SF-36 domain and summary score among all patients with available data at either time point (but not requiring data at both time points). Regression models using each SF-36 domain or summary score as a dependent variable were used to adjust the distribution of each treatment group to the age and gender distribution of the general population. Analysis of variance was used to compare the norm-based SF-36 scores for each treatment group to the general population for both the pre-and post-assessments.

To examine the association between pre-treatment HRQoL and risk of mortality, we conducted time to event analyses. Separate analyses were conducted based on short- and long-term lengths of follow-up time (1 and 5 years, respectively). Follow-up person-time was calculated as the number of days between treatment initiation and the recorded date of death or censoring. Patients were censored at the date of their last documented clinic visit or the cut-off date for the follow-up period, whichever occurred first. We artificially censored patients who were alive and continued follow-up past the 1 and 5 year periods at 365 or 1825 days after treatment initiation, respectively.

Treatment-specific analyses were conducted on patients who subsequently received HDM/SCT after their initial evaluation as well as on patients who subsequently received non-SCT chemotherapy regimens. Survival functions were plotted as Kaplan–Meier survival curves stratified by tertiles of PCS and MCS scores. Differences in the unadjusted survival functions were tested using log-rank tests. Cox proportional hazards regression models were conducted to estimate the hazard ratios (HR) and 95% confidence intervals (CIs) for the independent effect of baseline HRQoL on the risk of mortality. A stepwise selection approach, with the selection for entry and retention set at 5%, was used for determining the covariates (e.g., age, sex, time from diagnosis to evaluation, number of organs affected, cardiac involvement, kidney involvement, gastrointestinal involvement and liver involvement) for the final models. The proportional hazards assumption was assessed with Schoenfeld residuals and by testing interaction terms between time and each covariate found to violate the assumption. Significant interactions terms were retained in the final model to address evidence of non-proportionality.

Changes in HRQoL over time were examined using two approaches. Wilcoxon signed rank sum tests were used to test for significant differences between pre- and post-treatment SF-36 scores for each treatment group. Post-treatment assessments were ascertained at 18 months follow-up. Last observation carried forward was implemented if the patient completed a post-treatment assessment at least 6 months after treatment initiation, but did not complete an assessment that would approximate an 18-month follow-up visit.

All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Sample characteristics

Among the 1177 patients with treatment records and a treatment start date, approximately 50% completed an SF-36 survey during the appropriate time interval to serve as a baseline pre-treatment assessment of HRQoL. Patients who did not have a pre-treatment assessment were more likely to be non-white and slightly older than patients who had a pre-treatment assessment. On average, these patients spent a greater proportion of their day in bed, had a larger number of organs affected, had been diagnosed with AL amyloidosis for a longer period of time before being seen at BMC, and were less likely to receive HDM/SCT compared to patients with pre-treatment SF-36 assessments. Sample characteristics are presented in Table S1 by the availability of pre-treatment SF-36 surveys.

Mean age at the time of treatment initiation was 57 and 67 years for the groups of patients who received HDM/SCT and the non-SCT chemotherapy regimens, respectively ($P < 0{\cdot}001$). Greater proportions of patients who underwent HDM/SCT were married as compared to patients who received non-SCT chemotherapy regimens ($P < 0{\cdot}001$). Smaller proportions of patients who received HDM/SCT had cardiac involvement (45·7% vs. 64·6%, respectively; $P = 0{\cdot}001$). A greater proportion of patients who received HDM/SCT spent a smaller portion of their day in bed (74·9% vs. 57·9%, $P < 0{\cdot}001$), and on average, had fewer organs affected by AL amyloidosis ($P < 0{\cdot}001$). At baseline, significantly greater unadjusted mean SF-36 scores were observed among patients who received HDM/SCT as compared to those who received non-SCT chemotherapy regimens across all aspects of HRQoL with the exception of MH and MCS ($P < 0{\cdot}05$ for all). Demographic and disease characteristics for the primary study sample are reported in Table I by treatment group.

Pre- and post-treatment SF-36 scores for AL amyloidosis patients relative to US population norms

Statistically and clinically meaningful decrements in pre-treatment SF-36 scores were observed among patients who received a SCT across all domains and summary components

Table I. Comparison of demographics and clinical features of patients in the analytic sample by treatment group ($n = 574$).

	HDM/SCT ($n = 402$)	Non-SCT chemotherapy ($n = 172$)	*P*-value
Age at treatment initiation, mean years (SD)	57·2 (9·3)	67·2 (10·5)	<0·001
Male, %	60·0	64·5	0·302
Non-white, %	6·7	11·1	0·081
Education			0·101
<High school diploma	3·5	4·7	
High school graduate or GED	19·1	30·2	
Some college, Associates degree or Technical Certificate[2]	17·5	15·4	
Bachelor's degree (B.A, B.S)	24·6	25·5	
Graduate degree	35·3	24·2	
Married, %	84·1	75·5	<0·001
Time from diagnosis to treatment initiation, mean months (SD)	5·2 (5·3)	6·2 (14·4)	0·378
Performance status (% time spent in bed) at evaluation, % ($n = 389$)			<0·001
0–25%	74·9	57·9	
>25%	25·1	42·1	
Number of organs involved, mean (SD)			0·002
1–2	29·4	20·6	
3	27·4	19·4	
4	21·5	25·3	
≥5	21·7	34·7	
Types of organs/systems impacted, % yes			
Heart (Cardiac)	45·7	64·6	0·001
Kidney	82·8	70·9	0·825
Gastrointestinal	27·9	29·7	0·663
Liver	24·6	26·7	0·593
Nervous system	30·6	33·7	0·461
Soft tissue	17·9	25·6	0·036
SF-36 Domain Scores			
Physical functioning	40·2 (12·2)	32·4 (11·5)	<0·001
Role physical	38·5 (12·3)	34·2 (10·3)	<0·001
Bodily pain	49·2 (11·4)	45·9 (12·0)	0·003
General health	42·6 (10·2)	38·6 (10·0)	<0·001
Vitality	43·0 (12·0)	38·2 (10·6)	<0·001
Social functioning	41·8 (12·4)	37·3 (13·1)	<0·001
Role emotional	43·6 (13·5)	40·8 (14·5)	0·041
Mental health	47·1 (10·9)	45·8 (11·2)	0·2110
SF-36 Component Summary Scores			
Physical Component Summary	41·6 (11·5)	35·3 (10·2)	<0·001
Mental Component Summary	45·8 (11·2)	44·3 (12·1)	0·132

GED, general educational development; HDM, high dose melphalan; SCT, stem cell transplantation; SD, standard deviation.

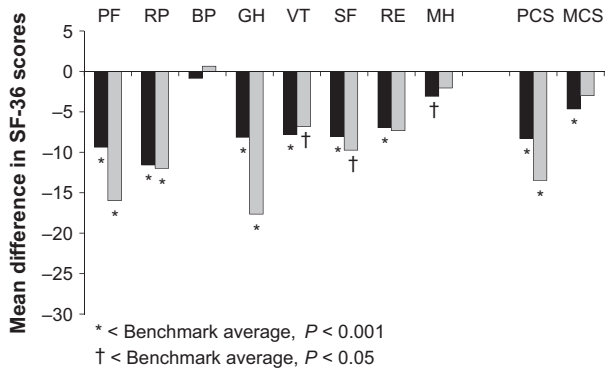

Fig 2. Deficits in pre-treatment HRQoL among AL amyloidosis patients relative to the general population. Black bars represent patients who received high dose melphalan and stem cell transplantation ($n = 402$); grey bars represent patients who received chemotherapy without stem cell transplantation ($n = 172$). BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality; HRQoL, health-related quality of life. [Correction added on 20 October 2017, after first online publication: The key for * has been corrected].

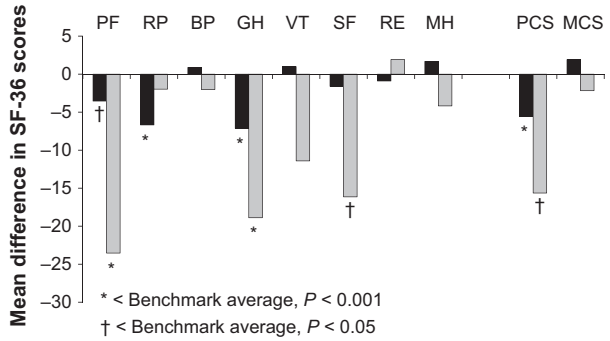

Fig 3. Deficits in post-treatment HRQoL among AL amyloidosis patients relative to the general population. Black bars represent patients who received high dose melphalan and stem cell transplantation ($n = 230$); Grey bars represent patients who received chemotherapy without stem cell transplantation ($n = 73$). BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality; HRQoL, health-related quality of life.

except the BP scale, relative to the general population ($P < 0{\cdot}05$ for all; Fig 2). Pre-treatment deficits in SF-36 were observed among patients who received non-SCT chemotherapy regimens in PF, RP, GH, VT and SF, as well as in PCS ($P < 0{\cdot}05$ for all; Fig 2). Among patients who received non-SCT chemotherapy regimens, pre-treatment HRQoL deficits were also clinically meaningful across all SF-36 domains and summary scores, with the exception of BP and MH.

Although patients who received HDM/SCT continued to report significant deficits at follow-up for PF, RP, GH and PCS, improvements in VT, SF, RE, MH and MCS following treatment led to comparable scores to the general population (Fig 3). Among patients who received non-SCT chemotherapy regimens, the deficits in GH increased over time; however, deficits in VT and RP scores were no longer significant following treatment (Fig 3).

Associations between HRQoL and risk of mortality

Mean scores, number of deaths and crude mortality rates are reported in Table S2 by tertiles of baseline PCS and MCS scores and treatment group. The unadjusted survival curves by baseline HRQoL (as measured by tertiles of baseline MCS and PCS scores) are also plotted for patients who received HDM/SCT and for patients who received non-SCT chemotherapy regimens based on 5 years of follow-up (Fig 4). Based on log rank tests, the differences among these curves were statistically significant across tertiles of PCS scores for both 1 and 5 years of follow-up data and in both treatment groups ($P < 0{\cdot}001$ for all). Survival functions did not significantly differ across tertile MCS scores for either follow-up period or treatment group.

As shown in Table II, there was an independent inverse relationship between PCS scores and risk of death for both treatment groups and follow-up periods after controlling for potential confounders. For every additional point in baseline PCS score (i.e., indicating better functioning), there was a 4–5% reduction in risk of death among patients who received HDM/SCT based on 1 and 5 years of follow-up, respectively ($P < 0{\cdot}001$ for both). Alternatively, worse pre-treatment PCS scores were associated with a greater risk of mortality. MCS, however, was not significantly associated with mortality among patients who received HDM/SCT for either follow-up period. Models for 1 and 5 years of follow-up additionally controlled for the number of organs affected and an interaction term between the number of organs affected and time to account for a violation to the proportionality assumption.

When we considered patients who received non-SCT chemotherapy regimens, we observed significant inverse associations between 1-year mortality and *both* PCS (HR = 0·91, 95% CI 0·85–0·96) and MCS (HR = 0·98, 95% CI 0·95–0·99) scores. In the final 1-year model, we controlled for cardiac and hepatic involvement, and we additionally included an interaction term between time and each covariate to address evidence of non-proportionality. A significant interaction term between PCS and time ($P < 0{\cdot}01$) was added to address a departure from the proportional hazards assumption. This interaction term provided additional information regarding how the relationship between PCS and mortality varies over the course of a year. Based on the model coefficients, we determined the approximate effect of PCS at several points in time. For instance, the main effect of PCS at baseline (week zero) was approximately a 9% reduction in mortality risk for each additional point in PCS score. Ten weeks after treatment initiation, there was only a 7% reduction in mortality risk for every one additional point in PCS score; by 26 weeks following treatment initiation, the magnitude of the association was even smaller (3% reduction in mortality risk). The overall effect

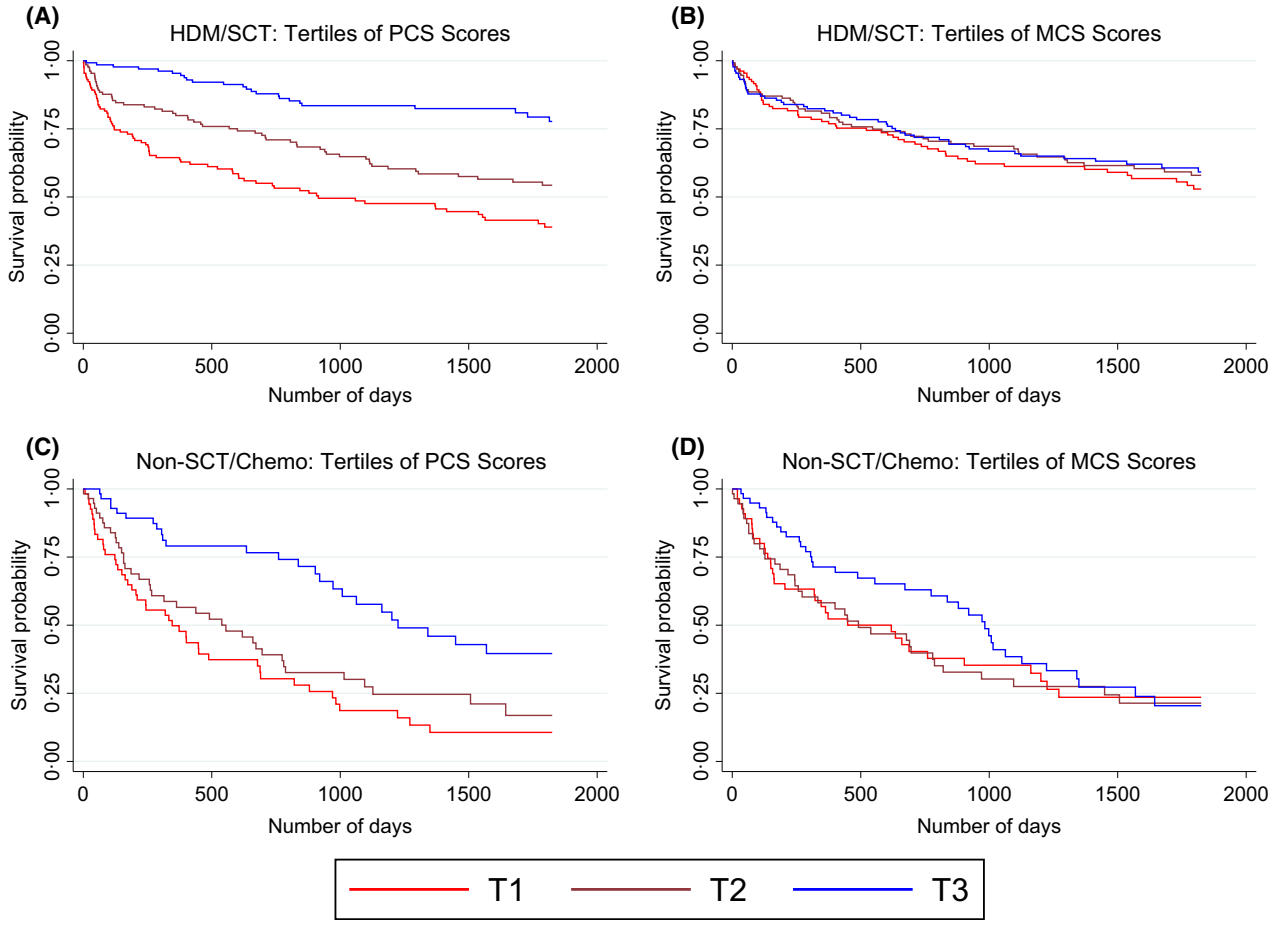

Fig 4. Kaplan–Meier survival curves for patients by level of HRQoL and treatment group based on 5 years of follow-up. HRQoL, as measured by the SF-36 physical component scores (PCS) and mental component scores (MCS), is categorized into tertiles where T1 represents the lowest tertile of scores and T3 represents the highest tertile of scores. Each panel represents the survival function for: (A) patients who received HDM/SCT by tertiles of PCS (Logrank test, $P < 0{\cdot}001$); (B) patients who received HDM/SCT by tertiles of MCS (Logrank test, $P = 0{\cdot}588$); (C) patients who received non-SCT chemotherapy regimens by tertiles of PCS (Logrank test, $P < 0{\cdot}001$); (D) patients who received non-SCT chemotherapy regimens by tertiles of MCS (Logrank test, $P = 0{\cdot}2928$). Chemo, chemotherapy; HDM, high dose melphalan; HRQoL, health-related quality of life; SCT, stem cell transplantation. [Correction added on 20 October 2017, after first online publication: MCS has been changed to PCS in figure label (C)].

estimate for PCS based on 5 years of follow-up data (HR = 0·95, 95% CI 0·92–0·99) was smaller than the effect estimate based on 1 year of follow-up data, further indicating that the effect may not be constant over time.

Changes in HRQoL

Significant improvements in HRQoL were found among patients who received HDM/SCT, as measured by significant mean differences in pre- and post-treatment PF, RP, BP, VT, SF, RE, MH and MCS scores ($P < 0{\cdot}05$ for all; Table III). In contrast, no significant improvements in HRQoL scores were observed among patients who received non-SCT chemotherapy regimens; however, a significant reduction in GH (40·0 vs. 34·1, $P < 0{\cdot}001$) occurred among these patients following treatment (Table III).

The significant differences in mean scores represent the averages observed in each treatment group and may not reflect patterns of individual-level change or changes within specific subgroups. To further explore the different nuances of changes in HRQoL, the overall percentages of patients who improved or worsened in each scale or summary score based on established MIDs for each treatment group are also reported in Table III. Among patients who received SCT/HDM, we observed greater proportions of patients who clinically improved than worsened across all aspects of HRQoL. For instance, nearly 4 times as many patients reported improvement in VT (45·1%) as compared to those who reportedly worsened (11·7%). The proportion of SCT/HDM patients who worsened in physical aspects of HRQoL ranged from 17·3 (RP) to 21·0 (GH). Few patients who received non-SCT chemotherapy regimens reported clinically meaningful improvement in PF and GH (6·5% and 3·2%, respectively). Similarly, notably high proportions of patients who received non-SCT chemotherapy reported clinical meaningful worsening for PF (35·5%) and GH (45·2%), as well.

Table II. Associations between baseline HRQoL and risk of death post-treatment among patients with AL amyloidosis by follow-up period and treatment group.

	HR (95% CI)	*P*-value
Treatment group: HDM/SCT (n = 402)		
Model 1 – 1-year post-treatment follow-up*		
PCS	0·95 (0·93, 0·98)	<0·001
Model 2 – 5-year post-treatment follow-up*		
PCS	0·96 (0·94, 0·98)	<0·001
Treatment group: non-SCT Chemotherapy(n = 172)		
Model 1 – 1-year post-treatment follow-up†		
PCS	0·91 (0·85, 0·96)	0·001
MCS	0·98 (0·95, 0·99)	0·028
Model 2 – 5-year post-treatment follow-up†		
PCS	0·95 (0·92, 0·99)	0·005

CI, confidence interval; HDM, high dose melphalan; HR, hazard ratio; MCS, mental component summary; PCS, physical component summary; SCT, stem cell transplantation.

*Adjusted for number of organs affected and an interaction term for number of organs affected × time.

†Adjusted for cardiac involvement, hepatic involvement, and the following interactions terms: cardiac involvement × time, hepatic involvement × time, and PCS × time.

Discussion

Overall, AL amyloidosis patients have broad HRQoL deficits across all areas of physical and mental functioning compared to the general population. The largest deficits were related to physical health status. We also observed a significant inverse association between HRQoL and risk of death following initiation of treatment for AL amyloidosis, namely HDM/SCT and standard non-SCT chemotherapy regimens. This result corroborates previous work reported by Seldin *et al* (2004) and further establishes the existence of pre-treatment levels of HRQoL, particularly physical health status, as a significant prognostic factor in patients with AL amyloidosis. These findings add to the body of evidence that supports the prognostic role of HRQoL, as measured by the SF-36, in survival for a variety of health conditions, including a wide range of cancers (Karvonen-Gutierrez *et al*, 2008; Grande *et al*, 2009). Additionally, our evidence suggests that this inverse association between physical aspects of HRQoL and risk of mortality may be strongest during short-term follow-up (i.e., within 1 year) in patients undergoing non-SCT chemotherapy.

Our longitudinal analyses of HRQoL extend existing research by examining HRQoL in patients who received different types of treatment for AL amyloidosis. These results indicate that changes in HRQoL may vary by treatment type over time. Among patients who received HDM/SCT, significant improvements in many aspects of HRQoL were observed following treatment that led to levels of functioning and well-being scores that were comparable to the general population, particularly in aspects related to mental health status. Smaller improvements or non-significant changes were observed among patients who received non-SCT chemotherapy regimens, indicating the need to better address both physical and mental HRQoL concerns within patients receiving this treatment regimen.

The availability of HRQoL data and medical records from this centre of excellence provided a unique opportunity to longitudinally examine HRQoL in AL amyloidosis. More specifically, these data allowed us to assess HRQoL as a potential prognostic factor for mortality risk and to examine change over time within different treatment regimens. To our knowledge, this is the only centre of excellence that has routinely collected HRQoL in AL amyloidosis patients for over 20 years. For a rare disease, this dataset provided a large sample of newly evaluated patients. Furthermore, these data provide insight into the real-world experiences of patients outside the regimented context of randomized controlled trials (RCTs).

As is typical of studies based on data collected in treatment centres that are not part of RCTs, generalizability of the study results may be limited because the majority of patients who received a non-SCT chemotherapy regimen did not have pre-treatment assessments of the SF-36 and most patients overall did not have multiple assessments of the SF-36. Our data indicate that patients who did not have a pre-treatment assessment may represent a group of patients with a more severe condition, in terms of longer duration of disease, worse physician-reported performance status and eligibility for HDM/SCT.

In addition, given the retrospective nature of the study design, our analyses were contingent on what data were available. For instance, the lack of scheduled time points for follow-up data collection further limited the sample sizes as well as the feasibility for certain analyses. To conserve data, we allowed follow-up assessments of HRQoL to occur during a fairly wide time interval (i.e., 6–18 months). This specific interval may not be sensitive to severe declines in functioning that may occur immediately following a treatment or declines that may resolve over the course of several months following treatment. Consequently, we recommend treatment centres standardize data collection for HRQoL at both short- and long-term scheduled time points to improve the availability of the data. In addition, we were unable to control for many standard markers for disease severity, such as the Mayo clinic cardiac biomarker stage or the New York Heart Association classifications. Based on previous studies, other measures of HRQoL, such as fatigue, have been identified as significant prognostic factors, even after controlling for Mayo clinic cardiac biomarker stage (Warsame *et al*, 2017). Furthermore, there is a high correlation between pre-treatment HRQoL and disease stage measures. Subsequently, it is very possible that additional information regarding disease staging would not have affected our results.

In this retrospective analysis of prospectively collected medical records, patients were not randomized to receive a particular treatment. These data indicate that patients who

Table III. Mean SF-36 scores among patients by time point and treatment group.

	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	*P*-value	% of patients with a clinically meaningful worsening at follow-up	% of patients with clinically meaningful improvement at follow-up
Treatment group: HDM/SCT (n = 162)					
SF-36 Norm-Based Scales					
Physical functioning	41·4 (11·9)	43·1 (12·3)	0·012	19·8	30·9
Role physical	39·6 (12·5)	42·8 (12·2)	0·003	17·3	39·5
Bodily pain	49·3 (11·1)	51·2 (10·6)	0·029	19·8	34·6
General health	42·8 (10·3)	43·2 (11·0)	0·441	21·0	24·1
Vitality	43·2 (12·3)	48·9 (11·8)	<0·001	11·7	45·1
Social functioning	43·1 (12·2)	47·6 (10·9)	<0·001	13·6	35·8
Role emotional	44·7 (13·0)	47·7 (11·4)	0·007	19·1	29·6
Mental health	47·1 (11·3)	50·8 (10·5)	<0·001	15·4	34·6
SF-36 Summary Scores					
Physical component summary	42·3 (11·4)	43·5 (11·7)	0·075	30·3	40·7
Mental component summary	46·3 (11·3)	50·9 (10·6)	<0·001	17·9	46·9
Treatment group: non-SCT chemotherapy (n = 31)					
SF-36 Norm-Based Scales					
Physical functioning	35·1 (12·8)	30·1 (12·0)	0·076	35·5	6·5
Role physical	36·4 (10·4)	40·0 (12·2)	0·086	19·4	38·7
Bodily pain	47·3 (12·0)	47·2 (11·8)	0·972	29·0	38·7
General health	40·0 (9·7)	34·1 (9·0)	<0·001	45·2	3·2
Vitality	38·6 (9·8)	38·9 (11·0)	0·945	16·1	25·8
Social functioning	39·5 (11·8)	40·5 (12·4)	0·476	19·4	25·8
Role emotional	42·8 (13·7)	45·8 (13·7)	0·342	16·1	32·3
Mental health	47·2 (11·6)	46·9 (11·3)	0·906	19·4	25·8
SF-36 Summary Scores					
Physical component summary	37·3 (12·5)	34·3 (10·4)	0·128	30·3	22·6
Mental component summary	45·5 (11·8)	47·9 (12·4)	0·242	17·9	29·0

HDM, high dose melphalan; SCT, stem cell transplantation; SD, standard deviation.

received HDM/SCT had significantly better pre-treatment levels of HRQoL as compared to patients who ultimately received non-SCT chemotherapy regimens. It is possible that pre-treatment levels of HRQoL may reflect clinical characteristics that determined subsequent treatment plans. This is not altogether surprising as patients who are eligible to receive HDM/SCT generally represent a healthier, lower risk subgroup (Dispenzieri *et al*, 2001). Furthermore, the availability of post-treatment assessments of HRQoL differed by treatment group. As such, we did not examine the effect of treatment group on risk of mortality or changes in HRQoL in any of our analyses. Comparing the magnitude of changes in HRQoL by treatment regimen from our treatment-specific models must be done with caution.

Despite these limitations, this is the first study, to our knowledge, to examine the association of pre-treatment HRQoL and risk of mortality for patients who received non-SCT chemotherapy regimens and longitudinal change in HRQoL for specific treatment regimens. Our findings indicate that pre-treatment levels of HRQoL, particularly related to physical well-being, may be a significant prognostic factor, regardless of treatment received. Consequently, incorporating clinical assessments of HRQoL, such as the SF-36, in clinical practice may provide valuable insight for clinicians treating rare conditions like AL amyloidosis. Given the complex relationships between treatment efficacy, HRQoL, and treatment adherence, future studies should examine the temporal relationships between treatment tolerability, changes in HRQoL, and health outcomes.

Acknowledgements

We gratefully acknowledge the numerous colleagues in the Amyloidosis Center, Cancer Clinical Trials Office, and Center for Cancer and Blood Disorders at Boston Medical Center who assisted with the multidisciplinary evaluation and treatment of the patients with AL amyloidosis. We also thank Tiffany Quock, Miyo Yokota, and Alexia Ng for reviewing analyses and drafts. This trial was partly supported by grants from Prothena Biosciences Inc. Editorial support was provided by ApotheCom, San Francisco, CA, USA and was funded by Prothena Biosciences Inc. Data gathering was funded by NIH PO1 HL68705 and the Amyloid Research Fund of Boston University School of Medicine.

Authorship contributions

VS, MB, KLM, SG, and MKW designed the study. MB, KLM, and MKW wrote the manuscript. KLM analysed data. SL provided data management. VS, MB, MKW, SG, and MS contributed expertise, critically reviewed the manuscript and gave final approval.

Disclosures of conflicts of interest

At the time of the original submission, MKW, MB, and KLM were full-time employees of Optum, Inc, which publishes the SF-36v2®, and received research funding from Prothena Biosciences Inc to conduct the study. SG was a full-time employee of the study sponsor, Prothena Biosciences Inc. Funds have been provided to the institution of VS, SL, and MS from Prothena Biosciences Inc, Takeda Pharmaceuticals, Janssen and Celgene.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Comparison of demographics and clinical features of patients by availability of SF-36 pre-treatment assessments (n = 1177).

Table S2. Number of deaths and crude mortality rates by treatment groups and quintile baseline PCS and MCS scores.

References

Bayliss, M., McCausland, K.L., Guthrie, S. & White, M.K. (2017) The burden of amyloid light chain amyloidosis on health-related quality of life. *Orphanet Journal of Rare Diseases*, **12**, 15.

Caccialanza, R., Palladini, G., Klersy, C., Cereda, E., Bonardi, C., Cameletti, B., Montagna, E., Russo, P., Foli, A., Milani, P., Lavatelli, F. & Merlini, G. (2012) Nutritional status independently affects quality of life of patients with systemic immunoglobulin light-chain (AL) amyloidosis. *Annals of Hematology*, **91**, 399–406.

Comenzo, R.L., Reece, D., Palladini, G., Seldin, D., Sanchorawala, V., Landau, H., Falk, R., Wells, K., Solomon, A., Wechalekar, A., Zonder, J., Dispenzieri, A., Gertz, M., Streicher, H., Skinner, M., Kyle, R.A. & Merlini, G. (2012) Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. *Leukemia*, **26**, 2317–2325.

Dispenzieri, A., Lacy, M.Q., Kyle, R.A., Therneau, T.M., Larson, D.R., Rajkumar, V., Fonseca, R., Greipp, P.R., Witzig, T.E., Lust, J.A. & Gertz, M.A. (2001) Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. *Journal of Clinical Oncology*, **19**, 3350–3356.

Falk, R.H., Comenzo, R.L. & Skinner, M. (1997) The systemic amyloidoses. *The New England Journal of Medicine*, **337**, 898–909.

Grande, G.E., Farquhar, M.C., Barclay, S.I. & Todd, C.J. (2009) Quality of life measures (EORTC QLQ-C30 and SF-36) as predictors of survival in palliative colorectal and lung cancer patients. *Palliative & Supportive Care*, **7**, 289–297.

Karvonen-Gutierrez, C.A., Ronis, D.L., Fowler, K.E., Terrell, J.E., Gruber, S.B. & Duffy, S.A. (2008) Quality of life scores predict survival among patients with head and neck cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **26**, 2754–2760.

Kyle, R.A. & Gertz, M.A. (1995) Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Seminars in Hematology*, **32**, 45–59.

Kyle, R.A., Linos, A., Beard, C.M., Linke, R.P., Gertz, M.A., O'Fallon, W.M. & Kurland, L.T. (1992) Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood*, **79**, 1817–1822.

Maruish, M.E. (2011) User's Manual for the SF-36v2 Health Survey, 3rd edn. QualityMetric, Inc., Lincoln, RI.

Merlini, G., Seldin, D.C. & Gertz, M.A. (2011) Amyloidosis: pathogenesis and new therapeutic options. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **29**, 1924–1933.

Palladini, G., Milani, P., Foli, A., Obici, L., Lavatelli, F., Nuvolone, M., Caccialanza, R., Perlini, S. & Merlini, G. (2014) Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. *Haematologica*, **99**, 743–750.

Pinney, J.H., Smith, C.J., Taube, J.B., Lachmann, H.J., Venner, C.P., Gibbs, S.D., Dungu, J., Banypersad, S.M., Wechalekar, A.D., Whelan, C.J., Hawkins, P.N. & Gillmore, J.D. (2013) Systemic amyloidosis in England: an epidemiological study. *British Journal of Haematology*, **161**, 525–532.

Sanchorawala, V. (2014) High dose melphalan and autologous peripheral blood stem cell transplantation in AL amyloidosis. *Hematology/Oncology Clinics of North America*, **28**, 1131–1144.

Seldin, D.C., Anderson, J.J., Sanchorawala, V., Malek, K., Wright, D.G., Quillen, K., Finn, K.T., Berk, J.L., Dember, L.M., Falk, R.H. & Skinner, M. (2004) Improvement in quality of life of patients with AL amyloidosis treated with high-dose melphalan and autologous stem cell transplantation. *Blood*, **104**, 1888–1893.

Ware, Jr, J.E., Kosinski, M. & Dewey, J.E. (2000a) How to Score Version 2 of the SF-36 Health Survey (standard and acute forms). QualityMetric Incorporated, Lincoln, RI.

Ware, Jr, J.E., Kosinski, M. & Gandek, B. (2000b) SF-36 Health Survey: Manual & Interpretation Guide. QualityMetric Incorporated, Lincoln, RI.

Warsame, R., Kumar, S.K., Gertz, M.A., Lacy, M.Q., Buadi, F.K., Hayman, S.R., Leung, N., Dingli, D., Lust, J.A., Lin, Y., Russell, S., Kapoor, P., Go, R.S., Kourelis, T., Gonsalves, W., Zeldenrust, S.R., Kyle, R.A., Vincent Rajkumar, S., Zemla, T., Sloan, J. & Dispenzieri, A. (2017) Hematology patient reported symptom screen to assess quality of life for AL amyloidosis. *American Journal of Hematology*, **92**, 435–440.