A prospective study of nutritional status in immunoglobulin light chain amyloidosis

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ABSTRACT

Weight loss is common in systemic immunoglobulin light chain amyloidosis but there are limited data on the impact of nutritional status on outcome. Using the Patient-Generated Subjective Global Assessment (PG-SGA) score, we prospectively examined nutritional status in 110 consecutive newly-diagnosed, treatment-naïve patients with immunoglobulin light chain amyloidosis attending the UK National Amyloidosis Centre. At study entry, 72 of 110 (66%) patients had a PG-SGA score of 4 or over, indicating malnutrition requiring specialist nutritional intervention. Number of amyloidotic organs, elevated alkaline phosphatase, presence of autonomic neuropathy and advanced Mayo disease stage were independently associated with poor nutritional status ($P<0.05$). Quality of life was substantially poorer among those with higher PG-SGA scores ($P<0.001$). Furthermore, PG-SGA score was a powerful independent predictor of patient survival ($P=0.02$). Malnutrition is prevalent and is associated with poor quality of life and reduced survival among patients with systemic immunoglobulin light chain amyloidosis. The PG-SGA score would be an appropriate tool to evaluate whether nutritional intervention could improve patient outcomes.

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Introduction

Amyloidosis is a protein deposition disease in which amyloid fibrils accumulate in the extracellular space and interfere with organ function.[1] In immunoglobulin light chain (AL) amyloidosis, the most commonly diagnosed systemic form of disease, the fibrils are derived from monoclonal immunoglobulin light chains, associated with an underlying B-cell dyscrasia. Virtually any organ may be directly infiltrated with AL amyloid deposits, leading to organ failure and death.[2] Typical clinical presentations include proteinuric renal dysfunction, cardiac failure, gastrointestinal disturbance and neuropathy, each of which may occur in isolation or simultaneously, depending on the site and extent of amyloid deposition. While there are as yet no therapies available that eliminate existing amyloid deposits, current treatment of AL amyloidosis aims to diminish new amyloid formation by reducing production of amyloidogenic immunoglobulin light chains with chemotherapy.[3]

Weight loss of more than 5%, the cause of which is likely multifactorial, is common and a predictor of poor survival among patients with AL amyloidosis.[2,4,5] Only one previous study has included a formal assessment of nutritional status prior to starting of chemotherapy and its relationship with quality of life (QOL) in patients with AL amyloidosis,[6] although several studies have examined this relationship in other patient groups.[7,8] Measurable and sustained improvements in QOL have been reported following treatment of AL amyloidosis with high-dose melphalan and autologous stem cell transplantation,[9] but the relationship between nutritional status, QOL and survival has not been prospectively examined in this disease.

This study aims to prospectively determine the impact of nutritional status on QOL and survival among 110 consecutive, newly diagnosed, treatment naïve individuals with systemic AL amyloidosis.

Design and Methods

Patient eligibility

All eligible patients attending the UK National Amyloidosis Centre (NAC) between April and December 2009 were invited to participate in the study. Inclusion criteria were: age 18 years and over, newly diagnosed, biopsy-proven AL amyloid, no prior chemotherapy but requiring chemotherapy for systemic AL amyloidosis, able to give written informed consent for entry into the study. Exclusion criteria were: localized or non-AL type amyloidosis.

Informed consent was obtained from each patient in accordance with the Declaration of Helsinki. Ethical approval for this prospective observational study was obtained from the Riverside Ethics Committee (REC Ref 09/H0706/27).

Study protocol

Each patient was assessed at baseline and then at 6-monthly intervals until study censor or death. The study was censored in September 2011, more than 18 months after enrollment of the last patient into the

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study. Baseline evaluation included: detailed clinical assessment including lying and standing blood pressure and nutritional status, biochemical tests of renal, hepatic and cardiac function, including 24-h proteinuria, NT proBNP and troponin T concentration, serum free light chain concentration and immunoelectrophoresis of serum and urine, electrocardiography and echocardiography. Organ involvement by amyloid was defined according to the international consensus criteria[10] and disease stage was defined according to cardiac biomarkers, as previously described by the Mayo clinic investigators.[11]

Nutritional assessments

All patients underwent a detailed nutritional assessment by a gastroenterologist (PTS) at their baseline visit to the NAC. Nutritional assessment included body mass index (BMI) and Patient–Generated Subjective Global Assessment (PG-SGA) score. BMI less than 20 kg/m^2 was taken to indicate 'nutritional risk' in accordance with malnutrition universal screening tool (MUST) risk stratification. The PG-SGA score, which has a high degree of inter-operator reproducibility, sensitivity and specificity,[12] consists of a questionnaire with two sections: one completed by the patient and the other by the clinician. Typical scores range from 0-35. Nutritional recommendations in relation to score are: 0-1, does not require nutritional input; 2-3, requires specialist nutritional education; 4-8, requires specialist nutritional intervention; ≥9, in critical need of symptom management together with specialist nutritional intervention.

Table 1. Patients' characteristics at baseline.

Characteristic	Value
Total number (n.) of patients	110
Age at recruitment; median years [interquartile range (IQR)]	66 (60, 74)
BMI at recruitment; median kg/m^2 (IQR)	25 (23, 29)
Gender; n. (%):	
Male	66 (60.0%)
Female	44 (40.0%)
Plasma cell dyscrasia; n. (%):	
Kappa	29 (26.4%)
Lambda	81 (73.6%)
Number of amyloidotic organs (by international amyloid consensus criteria); n. (%):	
1	35 (31.8%)
2	46 (41.8%)
≥3	29 (26.4%)
Kidney involvement; n. (%)	85 (77.3%)
Cardiac involvement; n. (%)	69 (62.7%)
Liver involvement; n. (%)	16 (14.6%)
Gastrointestinal involvement; n. (%)	5 (4.6%)
Autonomic neuropathy; n. (%)	16 (14.6%)
Peripheral neuropathy; n. (%)	10 (9.1%)
CKD stage; n. (%):	
≤3	86 (78.2%)
>3	24 (21.8%)
PG-SGA score; median (IQR)	9.5 (2, 14)
Dialysis; n. (%)	9/85 (10.6%)
Proteinuria; median g/L (IQR)	2.6 (0.6, 6.2)
Albumin (normal ≥35); median g/L (IQR)	33 (25.75, 40)
Bilirubin (normal <19); median ug/L (IQR)	7 (4, 11.5)
Gamma glutamyl transferase (normal ≤61); median U/L (IQR)	54 (28, 177)
Alkaline phosphatase (normal ≤129); median U/L (IQR)	105 (70, 175)
Mayo disease stage; n. (%):	
Stage 1	16 (14.5%)
Stage 2	35 (31.8%)
Stage 3	59 (53.7%)

QOL assessment

QOL was assessed by the EORTC QLQ-C30 questionnaire at the same time as the nutritional status assessment. The EORTC QLQ-C30 provides a functional score, a symptom score and a score for global health status.[13] High symptom scores represent a high level of symptomatology, high functional scores represent a high level of functioning, and high scores in global health status represent a good QOL.[14] The use of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 in patients with AL amyloidosis has been validated in a randomized controlled study of chemotherapy (UKATT study).[15]

Statistical analysis

Disease and patient specific factors associated with PG-SGA score were identified through linear regression analysis. Cut-off points for the factors were chosen by their clinical relevance or in line with previously published data. All factors of statistical significance (P<0.10) in univariable analyses and/or clinical significance were included in the multivariable analysis. Kaplan Meier analysis and log rank tests were used to compare patient survival. A Cox's proportional hazards regression analysis was performed to assess the independent effect on survival of PG-SGA. Pearson's correlation coefficient was determined to assess the linear relationship between QOL score and the actual value of PG-SGA. To overcome the problem of multiple testing for these coefficients, a significance level of 0.01 was used.

Data were analyzed using SPSS version 20 (IBM SPSS) and Stata v11 (StataCorp LP, USA).

Results and Discussion

Baseline patients' characteristics

One hundred and ten patients were enrolled into the study between April and December 2009. A further 3 eligible patients were offered study entry during this time period but declined. Patients' characteristics at baseline are summarized in Table 1. At baseline, median age was 66 years (range 42-88). Median time from symptom onset to baseline evaluation at the NAC was six months (range 0-28). The kidneys (85 patients) and heart (69 patients) were most commonly affected. Mayo disease stage at baseline was 1, 2 and 3 in 16, 35 and 59 patients, respectively.

Nutritional status by PG-SGA

At baseline evaluation, 66 (60%) patients stated that they had lost weight over the preceding six months. Food intake, as estimated by the patient, was less than normal over the preceding month in 61 (55%) patients, normal in 45 (41%) and increased in 4 (4%) cases. Diet was quantitatively reduced but remained qualitatively unchanged among 51 of 61 (84%) patients who had eaten less over the preceding month and was both quantitatively and qualitatively altered among the remainder. The main reasons for reduced food intake were reduced appetite (43%), altered taste of food (27%), early satiety (25%), and fatigue (21%).

Table 2. Median (IQR) QOL scores according to PG SGA score at baseline.

QOL parameter	Patient-Generated Subjective Global Assessment Score				
	0-1	2-3	4-8	≥9	*P*
Functional scale					
Global QOL	75 (54.2-83.3)	62.5 (50.7-66.7)	41.7 (33.3-66.7)	33.3 (16.7-43.8)	<0.001
Physical	89.2 (80.0-93.3)	66.7 (58.3-81.7)	60 (46.7-83.4)	40 (26.7-66.7)	<0.001
Role	100 (70.9-100)	50 (33.3-83.3)	33.3 (16.7-66.7)	16.7 (0-50)	<0.001
Emotional	91.7 (68.8-97.9)	83.3 (66.7-91.7)	83.3 (54.2-91.7)	66.7 (41.7-83.3)	<0.001
Social	100 (66.7-100)	83.3 (66.7-100)	66.7 (33.3-83.3)	33.3 (0-50)	<0.001
Cognitive	100 (83.3-100)	83.3 (79.2-100)	100 (83.3-100)	66.7 (50-100)	<0.001
Symptom scale					
Fatigue	16.7 (2.8-30.5)	33.3 (22.2-47.2)	44.4 (33.3-61.5)	77.8 (66.7-88.9)	<0.001
Appetite loss	0 (0-0)	0 (0-0)	33.3 (0-50)	66.7 (33.3-100)	<0.001
Nausea and vomiting	0 (0-0)	0 (0-0)	16.6 (0-33.3)	16.7 (0-33.3)	<0.001
Pain	0 (0-16.7.7)	0 (0-16.7)	0 (0-16.7)	33.3 (0-66.7)	<0.001
Dyspnea	33.3 (0-33.3)	66.7 (33.3-66.7)	66.7 (33.3-100)	50 (33.3-100)	0.34
Insomnia	16.7 (0-33.3)	33.3 (0-50)	33.3 (0-66.7)	33.3 (0-100)	0.001
Constipation	0 (0-0)	0 (0-33.3)	0 (0-16.7)	33.3 (0-16.65)	<0.001
Diarrhea	0 (0-0)	0 (0-0)	0 (0-33.3)	0 (0-33.3)	<0.03
Financial impact	0 (0-0)	0 (0-33.3)	0 (0-0)	0 (0-33.3)	0.01

The PG-SGA score was 0-1 in only 14 (13%) patients, with a requirement for nutritional education (score of 2-3) and nutritional intervention (score ≥4) in 24 (22%) and 72 (65%) patients, respectively; 57 (52%) patients were in critical need of nutritional intervention (score ≥9). There was no association between patient age or sex and PG-SGA score. Only 4 (<4%) patients had a BMI less than 20 kg/m^2 at baseline, and there was no correlation between BMI and nutritional state, as assessed by PG-SGA (r=-0.14).

Disease-related factors significantly associated with a higher PG-SGA score in multivariable regression analyses were alkaline phosphatase (ALP) outside the normal range, presence of autonomic neuropathy, greater number of amyloidotic organs, and higher Mayo disease stage.

QOL

There was a highly significant and consistent relationship between PG-SGA and QOL scores by EORTC QLQ-C30 (Table 2). Higher PG-SGA scores were associated with poorer overall QOL (*P*<0.001), including lower functional and higher symptom scores.

Patient survival

At censor, with a median follow-up period (with inclusion of deaths) of 1.2 years (range 0-2.4) years, 63 (57%) patients had died. PG-SGA score at baseline was the strongest independent predictor of patient survival in a model that included Mayo disease stage: HR 6.2; 95% CI: 1.2-32.4 for PG-SGA score 4-8 *versus* PG-SGA score 0-1 (*P*=0.03) and HR 6.4; 95% CI: 1.4-30.2 for PG-SGA score of 9 or over *versus* PG-SGA score 0-1 (*P*=0.02) (Table 3).

Conclusions

This prospective observational study highlights the fact that nutritional issues are prevalent among patients with AL amyloidosis, and are undoubtedly underdiagnosed.[5] Interestingly, fewer than 4% patients in this study had a low BMI (<20 kg/m^2) at baseline, despite a critical need for nutritional intervention in more than 50% of cases according to PG-SGA scores. The PG-SGA is a quick and easy tool to use making it an attractive nutritional assessment approach.[16]

The fact that both ALP above the normal range and advanced Mayo disease stage were independently associated with malnutrition suggests a contribution from hepatic and cardiac amyloidosis. Hepatic AL amyloid infiltration, typically associated with a large total body amyloid burden, has previously been reported to cause weight loss.[17] Cardiac cachexia is a well known complication of heart failure from a variety of causes,[18] and might be expected in amyloid cardiomyopathy.[5]

This study demonstrates a very strong association between malnutrition and almost all measures of poor QOL in patients with AL amyloidosis, confirming findings in previous studies in a range of malignant[19] and non-malignant diseases.[20] Furthermore, PG-SGA score at baseline was independently associated with survival, consistent with the recent findings of Caccialanza and colleagues,[6] as well as findings in patient cohorts with other malignant[21] and non-malignant diseases.[22] Interestingly, however, the PG-SGA was the only significant predictor of survival in a multivariable model incorporating, amongst other parameters, the Mayo disease staging system, which is the most commonly used and robust prognostic staging system in AL amyloidosis.[11] Although the absence of a difference in survival between patients with Mayo stage 1 and stage 2 disease in this study may initially appear surprising, it is likely to reflect the small number of cases. The Mayo staging system is most heavily influenced by presence of cardiac amyloidosis, the impact of which is unequivocal.[3] The PG-SGA,

Table 3. Factors at baseline associated with risk of death in patients with AL amyloidosis.

Characteristic	Univariable hazard ratio (95% CI)	Multivariable P	Hazard ratio (95% CI)	P
PG-SGA score				
0-1	1		1	
2-3	4.47 (1.00, 20.03)	0.05	3.34 (0.67, 16.72)	0.14
4-8	8.13 (1.77, 37.32)	0.007	6.17 (1.18, 32.42)	0.03
≥9	8.77 (2.11, 36.49)	0.003	6.37 (1.35, 30.15)	0.02
CKD stage				
1-3	1			
4-5	1.33 (0.74, 2.37)	0.35		
Mayo disease stage				
Stage 1	1		1	
Stage 2	1.71 (0.63, 4.68)	0.30	0.94 (0.32, 2.75)	0.91
Stage 3	3.60 (1.42, 9.13)	0.007	1.66 (0.59, 4.68)	0.34
ALP (U/L)				
<129	1			
>129	1.04 (0.62, 1.73)	0.89		
Amyloid peripheral neuropathy				
No	1			
Yes	1.13 (0.49, 2.62)	0.78		
Amyloid autonomic neuropathy				
No	1			
Yes	1.44 (0.75, 2.76)	0.28		
N. of organs involved by amyloid				
1-2	1	1		
≥3	1.81 (1.06, 3.07)	0.03	0.99 (0.54, 1.80)	0.97

however, takes into account other factors unlikely to be accounted for by the Mayo staging system, such as amyloidotic autonomic nerve and liver dysfunction, both of which were independently and significantly associated with higher PG-SGA scores in this study, and have previously been shown to negatively influence survival in AL amyloidosis.[23,24]

This prospective observational study provides a platform upon which to base future studies of nutritional intervention in AL amyloidosis. It would be useful to determine whether nutritional status affects tolerability and toxicity of treatment, and hence treatment response. Furthermore, whether malnutrition continues to impact on QOL after patients have completed chemotherapy for AL amyloidosis, and whether early and aggressive nutritional intervention can improve QOL and survival need to be prospectively studied. The PG-SGA is a good tool for examining these questions since it provides a score that can be included in analyses as a continuous variable, thus permitting potential identification on serial analyses of subtle changes in nutritional status.

In summary, prospective use of the PG-SGA, a simple nutritional assessment tool, in 110 newly diagnosed unselected consecutive patients with AL amyloidosis showed a strong association between malnutrition and both poor QOL and reduced survival. This study validates prospectively for the first time, an assessment tool with which to examine whether nutritional intervention in patients with AL amyloidosis influences the disease course.

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