bjh research paper

Outcome of autologous stem cell transplantation for AL amyloidosis in the UK

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Received 9 March 2006; accepted for publication 29 May 2006

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Summary

High-dose chemotherapy with autologous stem cell transplantation (SCT) is widely used as a treatment for systemic AL amyloidosis, but its efficacy has not been proved and it has substantial toxicity in this setting. We report here the outcome of 92 patients evaluated at the UK National Amyloidosis Centre who underwent SCT for AL amyloidosis between 1994 and 2004 in various British centres. Median age was 53 years and median of two organs were affected by amyloidosis. All-cause day 100 mortality [treatment-related mortality (TRM)] was 23% for the entire cohort, although this was substantially greater for patients treated from 1994 to 1998 (15/47, 32%) than subsequently (6/45, 13%). Independent factors significantly associated with TRM on multivariate analysis were: number of affected organs, performance status, serum albumin and age. Response of the underlying clonal disease, defined by ≥50% reduction in the aberrant serum-free light chain concentration, occurred in 83% of evaluable patients. Overall median survival was 5·3 years, and was 8·5 years among patients who survived beyond day 100. Despite recent refinements in patient selection, TRM remains substantial during SCT for systemic AL amyloidosis, and its place in the therapeutic armamentarium for this disease needs to be defined in randomised controlled clinical studies.

Keywords: amyloid, amyloidosis, melphalan, stem cell transplantation, treatment-related mortality.

AL is the commonest form of systemic amyloidosis in Western countries, affecting about 10 per million per year (Kyle *et al*, 1992). AL amyloid fibrils are derived from monoclonal immunoglobulin light chains, produced by plasma cell dyscrasias that are typically subtle. Historically, median survival was only 6–15 months from diagnosis (Kyle & Gertz, 1995) with fewer than 5% surviving 10 years (Kyle *et al*, 1999). No specific therapy yet exists and treatment is centred on suppressing the underlying clonal plasma cell disorder using chemotherapy derived from experience in myeloma. Benefit from this approach in AL was demonstrated in randomised controlled clinical trials of low-dose oral melphalan and prednisone, but in only 20–30% of patients (Skinner *et al*, 1996; Kyle *et al*, 1997).

Superior efficacy of high-dose melphalan with autologous stem cell transplantation (SCT) in myeloma (Attal *et al*, 1996) prompted use of this treatment in AL amyloidosis. Anecdotal reports (Majolino *et al*, 1993) were followed by open studies, notably including extensive experience in Boston (Comenzo *et al*, 1996, 1998; Skinner *et al*, 2004) where treatment-related mortality (TRM), defined as all-cause mortality during the first 100 d following therapy, has been about 13%, compared with <2–5% in myeloma. TRM has been even greater in multicentre studies, at 43% in a French series (Moreau *et al*, 1998) and 25% in an Autologous Blood and Marrow Transplant Registry series of 114 patients treated in 50 US centres (Vesole *et al*, 2003).

The severe toxicity of SCT in AL amyloidosis is due to multiple organ damage associated with heart, renal and liver failure, gastrointestinal (GI) bleeding and autonomic dysfunction (Comenzo & Gertz, 2002). Many separate TRM risk factors have been proposed, including adverse performance status (PS), cardiac amyloidosis, the number of amyloid-affected organs, renal failure, hepatic impairment and hypotension (Comenzo & Gertz, 2002; Gertz *et al*, 2002; Dispenzieri *et al*, 2004a; Mollee *et al*, 2004; Skinner *et al*,

  doi:10.1111/j.1365-2141.2006.06204.x

2004). Recent studies using rigorous patient selection in a single Canadian centre and in an Eastern Co-operative Oncology Group (ECOG) multicentre setting succeeded partially in reducing TRM (Gertz *et al*, 2004a; Mollee *et al*, 2004).

The claims that SCT is the most superior therapy in AL amyloidosis (Mehta, 2004) are based on uncontrolled studies performed in a handful of specialist US centres, along with a small series from France (Moreau *et al*, 1998) and Germany (Perz *et al*, 2004). In contrast, early data from a French randomised controlled multicentre trial suggest SCT is not superior to a combination of oral melphalan and dexamethasone (Jaccard *et al*, 2005). We report here the UK experience of SCT for AL amyloidosis, in which patients were treated at local hospitals and were evaluated systematically at the National Amyloidosis Centre (NAC). We placed particular emphasis on identifying factors associated with TRM.

Methods

Patients

The patients comprised all individuals evaluated at the NAC who underwent SCT for systemic AL amyloidosis in various hospitals throughout the UK between 1994 and 2004. Patients were excluded from analysis if they did not have amyloid involvement of at least one recognised major organ system, if the SCT was not their first, if they had symptomatic myeloma or if the single affected vital organ had been replaced by transplantation.

Diagnosis of AL amyloidosis was confirmed by histology and immunohistochemistry, and, where necessary, by exclusion of hereditary amyloid by sequencing the genes for transthyretin, fibrinogen Aα-chain, apolipoprotein AI and AII and lysozyme (Lachmann *et al*, 2002).

Determining the eligibility for SCT was left to the discretion of each patient's treating physician, and patients provided informed consent to undergo the procedure, acknowledging that it was of unproven efficacy.

Clinical assessments and outcome measures

Patients were evaluated at the NAC prior to SCT and six monthly thereafter. Primary outcome measures were TRM, defined as all-cause mortality by day +100 from return of stem cells, overall survival (OS), responses in terms of the underlying clonal plasma cell disease and amyloidotic organ function, and changes in amyloid load on serial serum amyloid P component (SAP) scintigraphy. Additionally, serum-free light chain (FLC) concentration (Freelite^{TM}; The Binding Site, Birmingham, UK) was determined three monthly from 2001 and retrospectively on available archived samples.

Amyloidotic organ involvement of the kidneys, heart, liver and nerves, and response to treatment were based on international consensus guidelines (Gertz *et al*, 2005). GI involvement was defined by compatible symptoms coupled with amyloid deposits on GI biopsy, diffuse lung involvement by imaging, and pleural involvement on biopsy. Syndromes of soft tissue involvement were symptomatic macroglossia, amyloid lymphadenopathy, skeletal muscle pseudohypertrophy, painful periarticular deposits and pathological bone fractures. Cutaneous or vascular amyloid, carpal tunnel syndrome and asymptomatic macroglossia were not classified as involvement. Factor X deficiency and adrenal insufficiency were assessed conventionally. Involvement by amyloid of one to five organ systems were determined in each patient, within the following categories: renal, cardiac, GI (including liver), nerves (peripheral and/or autonomic) and miscellaneous (significant soft tissue, lung, pleura, factor X deficiency, adrenal insufficiency). The extent of organ involvement was further evaluated by quantitative whole body (SAP) scintigraphy (Hawkins *et al*, 1990; Rydh *et al*, 1998). Regression of amyloid was defined as reduction of tracer uptake in affected organs and/or an increase in the blood-pool background signal, accumulation of amyloid by the converse, and steady state when no tracer localisation was unchanged (Hawkins *et al*, 1990; Rydh *et al*, 1998). Organ and scintigraphic responses were recorded as the best achieved at least 6 months after SCT until any of the following events: delivery of further treatment, relapse of clonal disease, death or cessation of follow up for any reason.

The underlying clonal disease was assessed by electrophoresis and immunofixation of serum and urine, and serum FLC assay (Gertz *et al*, 2005). Clonal disease response was assessed 3–6 months post-SCT, principally by changes in FLC concentration (Lachmann *et al*, 2003; Mead *et al*, 2004). FLCs were deemed valid for assessing response if the pre-SCT FLC κ/λ ratio exceeded the reference range (0·3–1·2) (Katzmann *et al*, 2002) and the concentration of the light chain class (i.e. κ or λ) containing the monoclonal component (hereafter called the monoclonal class) was elevated to more than twice the healthy polyclonal upper limit. A complete FLC response (CR) was defined as normalisation of both FLC classes or normalisation of the FLC ratio alone in the presence of renal failure causing retention of light chains. A partial response (PR) was defined as ≥50% but incomplete normalisation in the monoclonal class on serum FLC measurement. Minor response criteria have not been defined for FLC. Relapse of clonal disease from CR was defined as the reappearance of an abnormal FLC ratio coupled with doubling of the value of the monoclonal class, and from PR as ≥50% rise in the value of the monoclonal class. Serum and urine paraprotein response definitions were: CR if both became absent on electrophoresis and immunofixation, and PR if ≥50% reduction.

Stem cell harvesting and conditioning regimens

Stem cell transplantation, along with the regimens used for stem cell harvesting and conditioning, was performed in numerous UK haematology transplantation centres at the discretion of the treating physician.

Statistical analyses

Analysis was performed by using Statistical Package for the Social Sciences (SPSS; release 11 for Windows; SPSS, Chicago, IL, USA) and graphs prepared on Prism (Graphpad Prism version 4.03 for Windows; Graphpad, San Diego, CA, USA). All *P*-values are two-sided with a value of ≤0·05 being considered significant. TRM was defined as all-cause mortality to 100 d after the return of stem cells. TRM and non-TRM population differences were compared by chi-squared or Fisher's test for categorical variables, and unpaired *t*- and Mann–Whitney *U*-tests for normally distributed and nonparametric continuous variables respectively. Putative risk factors for TRM were examined by univariate and forward stepwise multivariate logistic regression to establish independent significance. In order to investigate factors affecting post-day 100 mortality, the Cox proportional hazards regression model was used to examine factors affecting OS in those patients surviving >100 d. Survival probabilities were calculated by the Kaplan–Meier method and comparisons were made using the log-rank test.

Results

A total of 92 patients assessed at the NAC underwent their first SCT for AL amyloidosis in the UK between 1994 and 2004. Annual transplant activity is summarised in Fig 1A. SCT was performed in 31 different centres, all but one of which had experience of the procedure in six or fewer patients with AL amyloidosis (Fig 1B). Conditioning regimens are known in 87 patients. Melphalan was used in all but one case: melphalan 200 mg/m^2 (Mel200) in 52, Mel140/total body irradiation (TBI) in four, Mel140 in 14, Mel80-100 in 13 and BEAM [carmustine (BCNU), etoposide, cytosine arabinoside, Mel140] in three cases. The remaining patient received cyclophosphamide/TBI. For the purpose of TRM analyses, treatment with Mel80-100 and Mel140 was categorised as intermediate dose, and the remainder as high dose (Gertz *et al*, 2004b). Pre-SCT induction therapy, in all cases a vincristine, adriamycin, dexamethasone (VAD)-like regimen, was given in 27 cases.

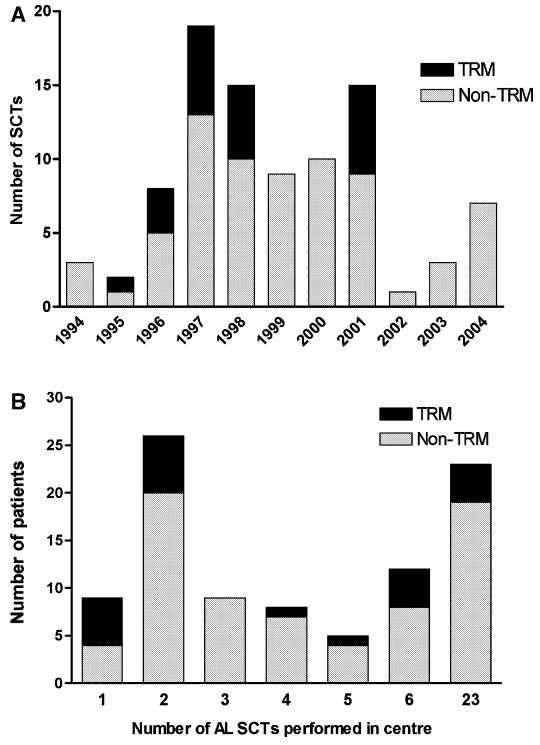

Fig 1. Stem cell transplantation activity and treatment-related mortality by (A) year and (B) volume in each centre.

Patient characteristics

The presenting features of the 92 patients are detailed in Table I. Mean age of patients at SCT was 53 years; 16 were aged 60–64 years and only four were ≥65 years. The median (mean) number of organs were affected by amyloid was two (2·0) and PS was one (0·9). Involved organs in the miscellaneous category (Table I) comprised severely symptomatic macroglossia (four cases), pathologic bone disease (five cases), amyloid lymphadenopathy (two cases), skeletal muscle pseudohypertrophy (one case), arthropathy (one case), lung (two cases) or pleural (one case) involvement, adrenal insufficiency (two cases) and factor X deficiency (one case). The aberrant light chain isotype was lambda in 66 cases (73%), and could not be determined in two patients.

Treatment-related mortality

Twenty-one patients (23%) died within 100 d from return of their stem cells. Patient characteristics in TRM and non-TRM groups are compared in Table I. The number of organs involved by amyloid correlated strongly with TRM ($P < 0{\cdot}0005$); all eight patients with four or five organs involved died by day 100, as did six of seventeen patients with three organs involved. Reduced PS, using ECOG criteria, was a similarly significant factor. Early mortality also was associated with male gender, lambda light chain isotype, any individual organ involvement except renal (which was almost universal), septal thickness, N-terminal pro-B natriuretic peptide (NT-ProBNP), amyloid features on electrocardiogram (ECG), proteinuria, alkaline phosphatase (ALP), SAP amyloid load, period when SCT performed, low serum albumin and not receiving pre-SCT induction therapy. These differences were also evident on univariate logistic regression (data not shown), with the exception of septal thickness, NT-proBNP and ALP; univariate analysis also suggested creatinine and NT-proBNP were associated with TRM at cut-off values of 200 μmol/l and 170 pmol/l respectively. Hepatic amyloid was a stronger TRM risk factor if SAP scan positivity was included as a marker of involvement.

Table I. Patient characteristics at SCT.

Patient characteristics	TRM group ($n = 21$)	Non-TRM group ($n = 71$)	*P*-value
Age (years)	55·8 (±7·9)	51·8 (±8·1)	0·053
Gender (male/female)	16/5	36/35	0·047
Diagnosis to SCT (months)	12·2 (±12)	12·9 (±14)	0·82
Performance status	1·6 (±0·8)	0·7 (±0·8)	<0·0005
0	1	36	
1	9	22	
2	8	11	
3	3	2	
Lambda/kappa	19/1	47/23	0·02
Number of involved organs*	3·0 (±1·2)	1·7 (±0·7)	<0·0005
1	3	30	
2	4	30	
3	6	11	
4	7	0	
5	1	0	
Organs individually			
Heart	14	26	0·02
Kidney	19	54	0·2
Liver/GIT (conventional criteria†)	13	17	0·003
Liver (by SAP scan)	16	24	0·003
Liver/GIT (scan or conventional)	17	26	<0·0005
Nerve	12	9	<0·0005
Other	4	15	1·0
Dominant presenting organ			
Renal	10	45	0·20
Cardiac	4	7	0·25
Liver/GIT	4	6	0·22
Neuropathy	2	2	0·22
Other	1	11	0·28
IVS (mm)	12·5 (10·1–14)	11·0 (9·4–13)	0·045
NT-proBNP (pmol/l)	135 (54–583)	44 (11–133)	0·003
ECG amyloid features present	16	21	<0·0005
Creatinine (μmol/l)	96 (81–242)	85 (75–118)	0·12
Serum albumin (g/l)	25·5 (20–31)	32·5 (24–40)	0·01
Proteinuria (g/d)	7·6 (3–11)	3·6 (0·6–6)	0·01
Bilirubin (μmol/l)	9 (8–10)	7 (5–10)	0·056
ALP (IU/l)	138 (90–178)	88 (65–108)	0·01
CRP (mg/l)	3 (1·3–6)	3 (2–7·5)	0·77
SAP scan large load	12	32	0·002
Any pre-induction therapy	6	29	0·09
Pre-SCT induction given	1	26	0·005
SCTs for AL performed in that centre			
1–2/3+	11/10	24/47	0·12
SCT era			
1994–98/1999–2004	15/6	32/39	0·047
Conditioning			
High/intermediate	9/8	5/19	0·11
Unknown	4	1	

Values given are mean (±SD), median (interquartile range) or *n*. *P*-value is for comparison between groups.

SCT, stem cell transplantation; TRM, treatment-related mortality; GIT, gastrointestinal tract; SAP, serum amyloid P component; IVS, interventricular septum; TBI, total body irradiation; ALP, alkaline phosphatase; CRP, C-reactive protein.

*Organs involved are kidney, heart, liver/GIT, nerve and other.

†Conventional criteria, i.e. ALP >1·5 × upper limit of normal or hepatomegaly >15 cm span.

Table II. Multivariate regression analysis of risk factors for treatment-related mortality.

Risk factor	Odds ratio (95% CI)	*P*-value
Number of involved organs (per organ)	3·8 (1·7–8·5)	0·001
Performance status (per grade)	3·4 (1·4–8·6)	0·01
Age (per decade)	2·5 (1·05–6·1)	0·04
Serum albumin (per 10 g/l reduction)	2·2 (1·02–4·8)	0·045

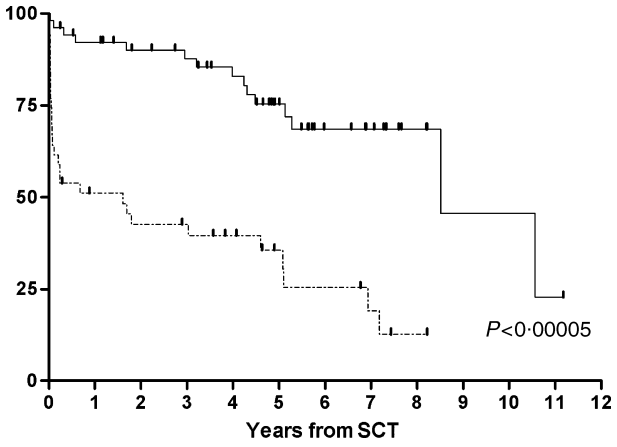

Fig 2. Overall survival from stem cell transplantation stratified by those with performance status (PS) 0-1 and 1-2 involved organs (solid line) *versus* others (dashed line).

The odds ratios for independently significant variables on multivariate regression analysis are shown in Table II, and emphasised further that number of involved organs and PS were powerful predictors of TRM. The combination of ECOG PS 0-1 and 1-2 amyloid-affected organs identifies a group of patients with substantially lower TRM compared with those who fail either criterion (Fig 2). The use of alternative criteria for defining organ involvement, including the omission of miscellaneous and/or renal involvement, separating out autonomic and peripheral neuropathy or liver and GI involvement, failed to define further the risk of TRM (data not shown). The apparent excess TRM in males, lambda light chain isotype, those who had not received pre-SCT induction therapy, the earlier (1994–98) cohort and at less experienced AL SCT centres was in each case explained by a poorer risk profile across the four independently significant variables listed in Table II.

Clone, clonal response and duration of clonal remission

Prior to SCT a serum paraprotein was detectable in 62% of cases, monoclonal urinary light chains [Bence Jones protein (BJP)] in 57%, and one or the other in 86%. Clonal response rates after SCT are given in Table III. The FLC response to SCT could be evaluated in 48 patients; the 44 patients whose FLC results were not valuable included the 21 early deaths, one whose baseline FLC failed to meet the criteria for assessment, six patients who were already in CR, 11 who had prior therapy and did not have a baseline FLC result immediately before SCT, and five in whom there was no post-SCT FLC value before their next therapy (four) or death (one). A complete FLC response occurred in 58% of evaluable patients, and a PR in a further 25%. Clonal response rates were not different between previously untreated, refractory or relapsed patients; notably, 13 of 14 evaluable patients who had relapsed or refractory clones achieved an FLC response to SCT. Conditioning regimen and light chain isotype did not appear to influence clonal response rates, noting that the series was small. Median duration of FLC remission following SCT was significantly longer in patients who achieved an FLC CR *versus* PR at 7 *versus* 2·8 years respectively. Conventional serum paraprotein and BJP response rates were somewhat lower than those for FLC (Table III). There were insufficient patients with disparate FLC *versus* paraprotein responses to assess possible differences in outcome.

Table III. Clonal responses to stem cell transplantation.

Clonal response marker(s)	*n*	CR	PR	NR
FLC	48	28 (58)	12 (25)	8 (17)
sPP/BJP*	52	19 (36)	18 (35)	15 (29)
FLC/sPP/BJP combined*	51	18 (35)	16 (31)	17 (33)

Values given are *n* (%) of the evaluable patients.
FLC, serum-free light chain; sPP, serum paraprotein; BJP, Bence Jones protein; CR, complete response; PR, partial response; NR, no response.
*Worst response of all parameters, where present.

Overall and post-day 100 survival

Median OS for the whole cohort was 5·3 years (Fig 3A), but was 8·5 years for patients who survived beyond day +100 (Fig 3B). Factors affecting mortality in the 71 patients who survived beyond day +100 were examined by Cox proportional hazards regression (Table IV): by univariate analysis, the number of amyloidotic organs, cardiac involvement, abnormal ECG, autonomic involvement, liver involvement by conventional criteria or on SAP scintigraphy and PS were all associated with significantly poorer OS. By contrast, univariate analysis attributed no significant effect on outcome to the total number of non-cardiac organs involved by amyloid, age, duration between diagnosis and treatment, light chain isotype, serum NT-proBNP, creatinine, albumin, bilirubin or ALP concentrations, proteinuria, renal/GI tract/peripheral nerve/other organ involvement, amyloid load on SAP scintigraphy or when SCT had been performed. Clonal response was of borderline significance ($P = 0{\cdot}07$), perhaps because the vast majority achieved at least a PR. The estimated 10-year survival for those surviving to day 100 and in CR post-SCT was 59%. On multivariate analysis, cardiac involvement was the strongest independent factor for reduced OS (Fig 3C), whilst autonomic neuropathy and liver involvement by conventional

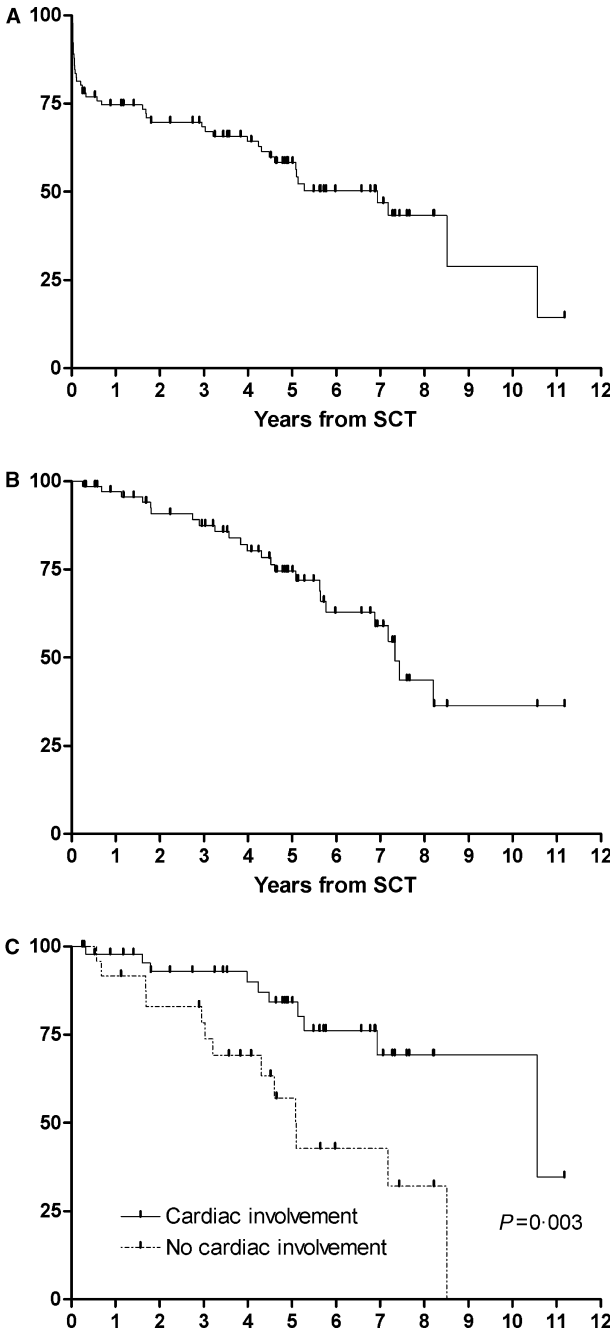

Fig 3. Overall survival of (A) all 92 patients receiving stem cell transplantation, (B) the 71 patients surviving to day +100, further stratified (C) according to the presence or absence of cardiac amyloidosis.

criteria or on SAP scintigraphy were the only other independently significant factors.

Response of amyloid-affected organs

The function of 48% of organs affected by amyloid improved either completely (22%) or partially (26%), evident at a median of 18 months following SCT. Amyloidotic organ function remained stable in another 32% of cases, and deteriorated in 20%, the latter mostly in association with poor function prior to SCT; numbers were insufficient to associate clonal and organ response. Cardiac amyloid improved less often than other affected organs (22% improved, 61% stable) ($P = 0{\cdot}005$). Whole body amyloid load on SAP scintigraphy decreased in 39 of the 60 cases (65%) in whom scans were performed before and after SCT, and remained stable in a further 30%.

Table IV. Univariate and multivariate analysis of pre-stem cell transplantation factors associated with overall survival in those patients surviving to day 100.

Prognostic factors	Odds ratio (95% CI)	*P*-value
Univariate analysis		
Age (per decade)	1·4 (0·8–2·4)	0·25
Lambda *versus* kappa	0·7 (0·24–1·6)	0·14
Performance status (per grade)	1·7 (1·05–2·9)	0·03
Number of involved organs	2·0 (1·2–3·5)	0·01
Organs (involved *versus* not)		
Heart	3·4 (1·4–7·9)	0·005
Kidney	1·5 (0·50–4·4)	0·49
Liver (conventional criteria)	1·9 (0·8–4·6)	0·16
Liver (by SAP scintigraphy)	2·5 (1·01–6·1)	0·049
Liver (scintigraphy or conventional)	2·9 (1·2–6·8)	0·02
Nerve (either)	2·6 (0·9–7·2)	0·07
Autonomic	3·3 (1·2–9·4)	0·025
IVS (per mm)	1·2 (1·0–1·4)	0·06
NT-proBNP (>170 pmol/l)	2·4 (0·75–7·5)	0·14
ECG amyloid features present	2·8 (1·1–6·7)	0·024
Creatinine (>200μmol/l)	1·4 (0·19–11)	0·72
Serum albumin (<35 g/l)	1·8 (0·61–5·1)	0·29
Proteinuria (>6 g/d)	2·3 (0·82–6·3)	0·12
SAP scan load (large *versus* small)	1·7 (0·64–4·5)	0·29
CR *versus* non-CR	0·4 (0·16–1·1)	0·07
Multivariate analysis		
Cardiac involvement	3·2 (1·4–7·5)	0·01
Autonomic neuropathy	3·4 (1·2–9·9)	0·02
Liver (scintigraphy/conventional)	2·8 (1·2–6·8)	0·02

SAP, serum amyloid P component; IVS, interventricular septal thickness; NT-proBNP, N-terminal pro-B natriuretic peptide; ECG, electrocardiogram; CR, complete response (on free light chain analysis).

Discussion

The encouraging overall outcome of SCT for AL amyloidosis in the UK has been variably tainted by high TRM. Median OS was 8·5 years among patients who survived beyond day 100, but TRM was 32% among the first 47 SCTs performed between 1994 and 1998, and 13% subsequently. High TRM has been encountered widely in this setting, and even the North American high-volume centres of excellence continue to report an incidence of around 13% (Gertz *et al*, 2002; Skinner *et al*, 2004). In non-specialist centres, TRM was 43% in a

French survey (Moreau *et al*, 1998), and 25% among 114 patients treated in 50 US centres (Vesole *et al*, 2003). Furthermore, only 33% of the latter patients had a haematological response, and observational studies do not always identify morbidity and mortality associated with stem cell mobilisation.

Overall survival in AL amyloidosis may be best among patients who attain CR (Lachmann *et al*, 2003; Skinner *et al*, 2004). Using FLC criteria 58% of evaluable patients in this UK series attained CR, and among those who survived beyond day 100, the median OS exceeded 10 years. The Boston group reported a CR rate of 40% 1 year after SCT using conventional haematological criteria (Skinner *et al*, 2004) and recently, a similar CR rate by FLC analysis was associated with median OS of over 8 years (Sanchorawala *et al*, 2005). Data from non-randomised studies therefore suggest SCT offers high rates of clonal remission in AL and good long-term outcome for those who survive the procedure. However, as these benefits come at the cost of many early deaths, vital questions remain as to whether TRM can be reduced, and whether there are efficacious but less toxic alternatives.

Even in uncomplicated myeloma, TRM during SCT is 1–2% in clinical trial populations (Child *et al*, 2003), and up to 5% overall (Reece *et al*, 2003). Candidate TRM risk factors in the present cohort of AL patients who were individually significant on multivariate analysis included number of amyloidotic organs, PS, serum albumin and age. The simple parameters of PS 0-1 coupled with only one or two affected organs delineated patients with a TRM of 6%, compared with 46% among patients who failed either criterion; furthermore, all of the low-risk patients whose serum albumin was >30 g/l survived SCT, whereas 71% of the high-risk patients with lower albumin concentration did not.

Many other factors have been reported to influence TRM, notably cardiac involvement (Saba *et al*, 1999; Gertz *et al*, 2000), although neither our series nor recent reports using cardiac biomarkers (Dispenzieri *et al*, 2004a) support this, possibly due to exclusion of such patients due to poor PS. The poor outcome of our few patients with significant renal failure, supported by similar reports, suggests serum creatinine >176–200 μmol/l is a contraindication to SCT (Gertz *et al*, 2002; Casserly *et al*, 2003; Fadia *et al*, 2003), as is advanced hepatic amyloidosis, because of its dire prognosis. Exclusion criteria based on the functional reserve of certain organs, and not the total number of involved organs, did not reduce TRM below 14% in a recent multicentre ECOG study (Gertz *et al*, 2004a). The concept of excluding patients who have a greater overall burden of amyloid measured by the number of affected organs is supported by SAP scintigraphy, in which a large whole body load was yet another variable associated with poor outcome in our study. In another analysis of our data, TRM occurred in only one of 44 patients who were in our low-risk group (PS 0-1 coupled with ≤2 affected organs) and had serum creatinine ≤200 μmol/l without a large amyloid load on SAP scintigraphy. Efforts to decrease TRM by lowering the dose of conditioning chemotherapy have reduced clonal response rates and overall outcome (Gertz *et al*, 2004b; Skinner *et al*, 2004).

Less intensive chemotherapy regimens for AL remain in widespread use (Guidelines Working Group of the UK Myeloma Forum, 2004). These include VAD, which in 229 patients, produced TRM of just 2%, a clonal disease response rate of 61%, and median OS at recent censor of 6·7 years (Goodman *et al*, 2005). Among 144 older, sicker patients who were treated with monthly cycles of intravenous melphalan 25 mg/m^2 and oral dexamethasone, the haematological response rate was 64%, TRM 10%, and median OS 3·5 years (Goodman *et al*, 2004). Palladini *et al* (2004) reported a 67% haematological response rate and excellent survival in 46 Italian patients who received oral melphalan and dexamethasone; a large US prospective trial cohort treated with dexamethasone and maintenance interferon showed a 53% haematological response rate though the median OS was only 2·6 years (Dhodapkar *et al*, 2004). A telling study from the Mayo Clinic found that historic patients who were retrospectively deemed 'eligible' for SCT, but who had actually received low intensity chemotherapy, had outcomes comparable with recent patients who did undergo SCT (Dispenzieri *et al*, 2001). Although a later case–control analysis by these investigators favoured SCT, questions about the comparison were raised (Dispenzieri *et al*, 2004b; Goodman & Hawkins, 2004). The only randomised controlled study of SCT *versus* less intensive chemotherapy, oral M-dex, was recently undertaken in 100 French patients; there was significantly higher TRM in the SCT arm whereas haematological response rates and survival were similar (Jaccard *et al*, 2005).

The UK experience emphasises the substantial toxicity of SCT in AL amyloidosis, and raises the possibility of decreasing this through even more stringent patient selection. The findings also stress that different factors influence TRM compared with subsequent survival. In particular, late mortality was more strongly associated with cardiac involvement than the number of amyloidotic organs or PS, and serum biomarkers may complement conventional cardiac parameters in this regard (Dispenzieri *et al*, 2004a). The simple strategy of selecting patients with good PS (<2) and only one or two amyloidotic organs has the potential to reduce TRM to rates approaching those seen in myeloma, and provides an attractive hypothesis to test in a randomised study, which would probably require international collaboration.

Acknowledgements

The authors acknowledge all the haematologists who treated and cared for these patients and to Richard Morris, Department of Primary care and Population Sciences, Royal Free and University College Medical School, for statistical advice. The work of the Centre for Amyloidosis and Acute Phase Proteins is supported by grants from the Medical Research Council (UK), The Wellcome Trust, the Wolfson Foundation and NHS Research and Development Funds.

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