Sequential cardiac and autologous stem cell transplantation for systemic AL amyloidosis

**Short title:** CARDIAC AND SCT FOR AL AMYLOIDOSIS

Julian D. Gillmore, Hugh J. Goodman, Helen J. Lachmann, Mark Offer, Ashutosh D. Wechalekar, Jayshree Joshi, Mark B. Pepys, and Philip N. Hawkins

From the National Amyloidosis Centre, Centre for Amyloidosis & Acute Phase Proteins, Department of Medicine (Hampstead Campus), Royal Free and University College Medical School, London, United Kingdom.

Supported by MRC Programme Grant G97900510 (M.B.P. & P.N.H.), Wolfson Foundation, UCL Amyloidosis Research Fund and NHS Research and Development Funds.

J.D.G. performed research, analyzed data and wrote paper; H.J.G. performed research and analyzed data; H.J.L. performed research; M.O. performed research; A.D.W. performed research and wrote paper; J.J. performed research, M.B.P. designed research and wrote paper; P.N.H. designed and performed research and wrote paper.

**Word counts:** text 1200, abstract 152

**Scientific heading:** Clinical Observations, Interventions, and Therapeutic Trials

**Correspondence:** Dr J.D. Gillmore, National Amyloidosis Centre, Department of Medicine, Royal Free and University College Medical School, Rowland Hill St, London NW3 2PF, United Kingdom.

Tel: +44 20 7433 2800; fax: +44 20 7433 2817; e-mail: j.gillmore@medsch.ucl.ac.uk
Extensive cardiac amyloid deposition in systemic AL amyloidosis is associated with a grave prognosis. Cardiac transplantation is rarely performed due to the systemic and progressive nature of the disease. Patients with severe cardiac amyloid are ineligible for the preferred treatment of melphalan chemotherapy with stem cell rescue (SCT) due to the high risk of treatment-related mortality. Cardiac transplantation followed by SCT was performed in 5 patients with AL amyloidosis and predominant cardiomyopathy. Patients were followed for a median (range) of 95 (37-118) months from diagnosis. At censor, three of 5 patients were well without evidence of intra or extra-cardiac amyloid accumulation, and median overall survival by Kaplan-Meier estimate was not reached. Two patients died of progressive amyloid 33 and 90 months after cardiac transplantation following relapse of their underlying plasma cell dyscrasia. Cardiac transplantation followed by SCT is feasible in selected patients with cardiac AL amyloidosis and may confer substantial survival benefit.
Introduction

Systemic AL amyloidosis is a severe progressive disease with a median survival from diagnosis of 24-36 months.\textsuperscript{1} Symptomatic cardiac involvement is associated with a particularly poor prognosis, typically 9 months.\textsuperscript{2-4} Treatment is with chemotherapy aimed at suppressing the underlying monoclonal B cell dyscrasia.\textsuperscript{5} Only 20-30\% of patients respond to oral melphalan and prednisolone.\textsuperscript{3,6} Response rates and overall survival are improved with high dose melphalan and autologous stem cell transplantation (SCT) although this incurs substantial treatment-related mortality (TRM).\textsuperscript{7-10} Cardiac amyloidosis is an important risk factor for TRM\textsuperscript{9} and patients with advanced cardiomyopathy are ineligible for SCT.\textsuperscript{11}

Heart transplantation in AL amyloidosis, first reported in 1988,\textsuperscript{12} remains controversial since amyloid can be expected to recur in the graft and accumulate in other organs with fatal consequences within 3-5 years.\textsuperscript{13}

We present here the outcome of cardiac transplantation followed by SCT in 5 patients with systemic AL amyloidosis who were evaluated at the UK National Amyloidosis Centre, highlighting the feasibility of this approach in selected patients with systemic amyloidosis and predominant cardiomyopathy.

Materials and methods

Between 1992-2005, 5 patients evaluated at the UK National Amyloidosis Centre (NAC) with advanced AL amyloid cardiomyopathy and limited extra-cardiac amyloid were selected to undergo cardiac transplantation followed by SCT.

The diagnosis of AL amyloidosis was established histologically and supported by demonstration of a plasma cell dyscrasia in each case. The extent and course of
extra-cardiac visceral organ involvement by amyloid was evaluated by serial whole body $^{123}$I-labeled serum amyloid P component (SAP) scintigraphy.\textsuperscript{14-16}

Evaluation, performed 6-12 monthly at the NAC, included clinical assessment, electrocardiography, echocardiography, bone marrow aspirate and trephine, and full biochemical analysis of serum and urine. After 2003, serum free light chain (FLC) concentration was determined in all patients and where necessary, was performed retrospectively on stored sera.\textsuperscript{17} The novel medical care described here was performed with informed consent from each patient in accordance with the Declaration of Helsinki.

**Results**

**Subjects**

Patient characteristics at presentation are shown in Table 1. A substantial monoclonal FLC excess was present in each case, but no patient had evidence of lytic bone lesions.

A single patient, (2), received chemotherapy prior to cardiac transplantation comprising three 28 day cycles of 25 mg/m$^2$ intravenous melphalan on day +1 and oral dexamethasone 20 mg daily on days +1 to +4.

**Cardiac transplantation**

Cardiac transplantation, performed in 4 different centers, was uncomplicated in 3 cases; one patient had a tonic-clonic convulsion and the other hemorrhaged precipitating transient acute renal failure. Initial immunosuppression was with cyclosporin A, azathioprine and prednisolone in 4 cases and additional anti-thymocyte
globulin in patient 5. All acute rejection episodes responded to intravenous methylprednisolone (Table 1).

**Chemotherapy and stem cell transplantation**

The median time from cardiac transplantation to SCT was 13 months (range 10-24), during which time SAP scintigraphy demonstrated accumulation of extra-cardiac amyloid in each patient, but there was no evidence of amyloid in the cardiac allografts. Patient 1 received 6 cycles of oral melphalan (total dose 504 mg) and prednisolone prior to SCT, which on retrospective FLCs testing was ineffective.

Azathioprine was substituted by an increase in prednisolone dosage for stem cell harvesting and the duration of the SCT. Stem cells were mobilized for apheresis collection with G-CSF alone in 4 patients and cyclophosphamide and G-CSF in the remaining patient. Conditioning comprised melphalan, median dose 140 mg/m² (range 140-200), and engraftment occurred successfully in all 5 patients. Three SCTs were uncomplicated whereas patients 4 and 5 developed fungal pneumonia and reversible dialysis-dependent acute renal failure respectively, but there was no TRM.

**Response to chemotherapy and stem cell transplantation (SCT)**

SCT resulted in complete normalization of FLCs in patient 3 and a ~90% response in patient 5 (Figure 1A), which were sustained at the time of censor. Neither patient has clinical, biochemical or echocardiographic evidence of cardiac graft amyloid or of extra-cardiac amyloid deposition more than 9 years after cardiac transplantation. Furthermore, amyloid has not been detected histologically in routine yearly post-transplant cardiac biopsies in either case.
Patient 2 showed only a minor FLC response and relapsed within 10 months of SCT but had a substantial and sustained FLC response to subsequent high-dose dexamethasone (40 mg daily, days 1-4) (Figure 1A). At the time of censor, he was clinically well without evidence of amyloid in the cardiac allograft.

The plasma cell dyscrasia relapsed after an initial response to SCT in two patients. Patient 1 was clinically well until relapse, 56 months after SCT, whereupon his general condition deteriorated rapidly. In patient 4, a transient partial response to SCT was followed by a progressive rise in the aberrant FLC and ultimately fatal amyloid accumulation in the liver, spleen and cardiac allograft. In both patients, relapse of the plasma cell dyscrasia was accompanied by development of characteristic amyloid cardiomyopathy on echocardiography and a substantial rise in serum NT-ProBNP (Figure 1B).

Survival

Despite median follow-up from diagnosis of 95 months (range 37-118), median overall survival by Kaplan-Meier estimate was not reached at censor; the projected mean (CI) patient survival from diagnosis, cardiac transplantation and SCT was 95.5 (68-123), 91.1 (64-118) and 76.4 (47-105) months respectively. Patients 1 and 4 died of progressive amyloidosis following relapse of the underlying plasma cell dyscrasia, 95 and 37 months after diagnosis of amyloid and 90 and 33 months after cardiac transplantation respectively.

Discussion

This is the first reported series of cardiac transplantation followed by autologous peripheral blood SCT for systemic AL amyloidosis, and illustrates its feasibility and
potential for prolonged survival in selected patients presenting with predominant cardiomyopathy.

Cardiac transplantation in AL amyloidosis is controversial due to the systemic and progressive nature of the disease.\textsuperscript{13,18} Five year survival following cardiac transplantation was recently reported as 38\% in amyloidosis versus 67\% in all other conditions.\textsuperscript{18} A previous series reported 4-year patient survival of 39\% and development of allograft amyloid in 4 of 9 recipients.\textsuperscript{19} However, 3 of 5 (60\%) patients in the present series who had sustained suppression of their clonal disease after chemotherapy, had normal performance status and no evidence of cardiac or extra-cardiac amyloid accumulation at the time of censor (64, 116 and 118 months after diagnosis of amyloidosis).

All 5 patients reported here were carefully selected for the absence of clinically significant extra-cardiac amyloid and cardiac transplantation was therefore expected to restore normal functional status, thereby permitting SCT to be performed afterwards with relatively little risk of TRM.\textsuperscript{11}

The degree by which monoclonal light chain production needs to be suppressed to prevent amyloid deposition in transplant hearts is unknown, although the lack of amyloid in the allografts of the 3 surviving patients in this series suggests that an 80\% reduction in the aberrant serum FLC concentration is sufficient. The two patients who died, 90 and 33 months after heart transplantation, did so after their clonal disease had relapsed which was accompanied by accumulation of amyloid in the cardiac allograft and elsewhere.

Although our experience demonstrates the feasibility and substantial survival benefit of sequential cardiac transplantation and SCT in AL amyloidosis, only a small minority of patients with severe cardiac involvement are likely to benefit from this
tandem approach. To date, these are the only 5 patients of more than 2500 individuals with AL amyloidosis who have attended the NAC over the past 10 years to have been considered eligible for this tandem approach by all their attending medical and surgical specialists.
Acknowledgments

We are grateful to the following physicians and surgeons who contributed to the care of these patients; Dr J. Parameshwar, Papworth Hospital, Cambridge, UK, Professor J.F. Apperley, Hammersmith Hospital, London, UK, Dr F. Serfontein, Sinoville, South Africa, Professor P. Jacobs, Cape Town, South Africa, Mr P.C. Braidley, Northern General Hospital, Sheffield, UK, Dr E.A. Vandenberghe, Royal Hallamshire Hospital, Sheffield, UK, Dr L.J. Olsen, Mayo Clinic, Minnesota, USA, Dr M.A. Gertz, Mayo Clinic, Minnesota, USA.
References


Table 1. Patient characteristics at presentation, and peri-cardiac transplant course

<table>
<thead>
<tr>
<th>Sex, age at diagnosis of amyloid</th>
<th>Time from amyloid Dx to cardiac Tx</th>
<th>NYHA class heart failure</th>
<th>ECHO IVS/LVPW thickness (mm)</th>
<th>Creat / proteinuria (µmol/L / g/24 h)</th>
<th>Plasma cell dyscrasia</th>
<th>ChemoRx prior to cardiac Tx</th>
<th>Post-cardiac transplant in-patient stay (days)</th>
<th>Number of rejection episodes / timing after cardiac Tx (weeks)</th>
<th>ISHLT rejection grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>(years)</td>
<td>(months)</td>
<td>(mm)</td>
<td></td>
<td></td>
<td>%PC FLC(k) / FLC(A) κ/λ ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M, 56</td>
<td>4</td>
<td>IV</td>
<td>18 / 17</td>
<td>Sm / Sp, kid</td>
<td>97 / 0.1</td>
<td>7 / 349 / 44.3 / 7.9</td>
<td>-</td>
<td>14 / 14 / 14 / 14</td>
</tr>
<tr>
<td>2</td>
<td>M, 59</td>
<td>9</td>
<td>IV</td>
<td>19 / 17</td>
<td>Sm / Sp, kid</td>
<td>89 / 0.17</td>
<td>7 / 5.1 / 129 / 0.04</td>
<td>mel / dex</td>
<td>22 / 22 / 22</td>
</tr>
<tr>
<td>3</td>
<td>M, 44</td>
<td>2</td>
<td>IV</td>
<td>17 / 18</td>
<td>Sm / nil</td>
<td>108 / 0.6</td>
<td>7 / 4.0 / 342 / 0.01</td>
<td>-</td>
<td>24 / 24 / 24</td>
</tr>
<tr>
<td>4</td>
<td>M, 38</td>
<td>4</td>
<td>IV</td>
<td>15 / 15</td>
<td>Sm / Sp</td>
<td>113 / 0.3</td>
<td>15 / 1.4 / 479 / 0.00</td>
<td>-</td>
<td>28 / 28 / 28</td>
</tr>
<tr>
<td>5</td>
<td>M, 53</td>
<td>8</td>
<td>IV</td>
<td>17 / 16</td>
<td>Sm / Sp, kid</td>
<td>119 / 0.6</td>
<td>&lt; 5 / 1040 / 23.8 / 43.7</td>
<td>-</td>
<td>30 / 30 / 30</td>
</tr>
</tbody>
</table>

Dx indicates diagnosis; Tx, transplant; NYHA, New York Heart Association; IVS, intraventricular septum; LVPW, left ventricular posterior wall; SAP, serum amyloid P component; Sm, small; Sp, spleen; kid, kidneys; Creat, serum creatinine; PC, plasma cells in bone marrow; FLC, free light chain; ChemoRx, chemotherapy; mel/dex, cyclical intravenous melphalan and oral dexamethasone (see text); ISHLT, International Society of Heart and Lung Transplantation.
Legend to figure

**Figure 1. Serial serum free light chain (FLC) and NT-ProBNP concentration.**

Each line represents a single patient; alive at censor (open symbols) and dead (shaded symbols). (A) Response of the FLC concentration to chemotherapy. FLC concentration fell after SCT to < 50% of pre-treatment levels in 4 patients. Patient 3 had a fall in FLC concentration after cardiac transplantation and prior to SCT, further consolidated by SCT. Patient 2 had a poor initial FLC response to SCT and then relapsed but responded to commencement of high dose dexamethasone (arrow). Patients 1 and 4 had a FLC relapse associated with progressive intra and extra-cardiac amyloid accumulation and died. (B) Serial serum NT-proBNP concentration. NT-ProBNP fell after cardiac transplantation (timing of which was between the dotted vertical lines) in the 4 patients in whom it was measured. Relapse of the plasma cell dyscrasia and accumulation of amyloid in the cardiac allograft and major viscera in 2 patients was associated with a marked rise in NT-ProBNP and patient death.
Figure 1
Sequential cardiac and autologous stem cell transplantation for systemic AL amyloidosis

Julian D Gillmore, Hugh J Goodman, Helen J Lachmann, Mark Offer, Ashutosh D Wechalekar, Jayshree Joshi, Mark B Pepys and Philip N Hawkins