Cardiac Transplantation Followed by Dose-Intensive Melphalan and Autologous Stem-Cell Transplantation for Light Chain Amyloidosis and Heart Failure

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Background. Patients with light chain (AL) amyloidosis who present with severe heart failure due to cardiac involvement rarely survive more than 6 months. Survival after cardiac transplantation is markedly reduced due to the progression of amyloidosis. Autologous stem-cell transplantation (ASCT) has become a common therapy for AL amyloidosis, but there is an exceedingly high treatment-related mortality in patients with heart failure.

Methods. We developed a treatment strategy of cardiac transplant followed by ASCT. Twenty-six patients were evaluated, and of 18 eligible patients, nine patients underwent cardiac transplantation. Eight of these patients subsequently received an ASCT.

Results. Six of seven evaluable patients achieved a complete hematologic remission, and one achieved a partial remission. At a median follow-up of 56 months from cardiac transplant, five of seven patients are alive without recurrent amyloidosis. Their survival is comparable with 17,389 patients who received heart transplants for nonamyloid heart disease: 64% in nonamyloid vs. 60% in amyloid patients at 7 years (P=0.83). Seven of eight transplanted patients have had no evidence of amyloid in their cardiac allograft.

Conclusions. This demonstrates that cardiac transplantation followed by ASCT is feasible in selected patients with AL amyloidosis and heart failure, and that such a strategy may lead to improved overall survival.

Keywords: Amyloid, Cardiac amyloidosis, Stem-cell transplantation.

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Systemic AL amyloidosis is a plasma cell dyscrasia (PCD) marked by the progressive systemic deposition of monoclonal immunoglobulin light chains as amyloid fibrils leading to organ failure and death (18). Conventional chemotherapy for this disease only modestly improves outcomes, increasing median survival to only 18 to 24 months (1–4). The overall survival of these patients has been improved by the use of high-dose chemotherapy and autologous stem-cell transplantation (ASCT), leading to a median survival of 4.6 years (5–7). Patients with AL amyloidosis who present with severe heart failure due to cardiac amyloidosis have particularly poor prognosis, with a median survival of only 6 months and a 100% mortality at 2 years (1, 3, 8–10). In addition, patients with any degree of cardiac involvement suffer from a substantially higher ASCT-related mortality with survival outcomes inferior to those without cardiac involvement (5, 11) and, therefore, are currently precluded from undergoing ASCT at most centers.

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In 1988, cardiac transplantation began to be used to treat AL amyloidosis patients with overt heart failure (12). However, survival beyond 30 months in transplant recipients was markedly reduced because of progressive amyloid deposition causing severe organ dysfunction, often involving the cardiac allograft (12–15). Hosenpud et al. (13) reported a 4-year survival rate of 39% in these cardiac transplant recipients, with significant systemic progression of amyloidosis in the majority. This led to the virtual cessation of cardiac transplantation as a therapeutic option for these patients. More recently, the Heart Transplant Centers in Europe consortium reported a 5-year survival of 38% in recipients with AL amyloidosis compared with 67% in recipients with heart failure due to nonamyloid causes (14). Based on these discouraging outcomes and the shortage of donor organs, amyloid heart disease has been considered a contraindication for orthotopic heart transplantation (OHT).

In 2004, Skinner et al. reported a complete hematologic response, defined as no evidence of an underlying PCD 1 year after treatment, in 40% of patients with primary AL amyloidosis who received high-dose melphalan followed by ASCT (5). This increased the possibility of achieving long-term survival without progressive amyloid deposition, if amyloid patients undergoing cardiac transplantation were subsequently given high-dose chemotherapy and ASCT (16). Recently, cardiac transplantation followed by ASCT has been shown to be feasible with an apparent improvement in survival in carefully selected patients with AL amyloidosis presenting with severe heart failure (17, 18).

In 2000, we developed a treatment strategy for patients with systemic AL amyloidosis and heart failure consisting of cardiac transplantation followed by ASCT, with the goal of defining the safety and efficacy of this treatment approach. In this study, we report the outcomes of 26 patients with AL amyloidosis complicated by severe heart failure referred to the Massachusetts General Hospital for sequential cardiac transplantation and dose-intensive melphalan and ASCT.

**MATERIALS AND METHODS**

**Patients**

The study population consisted of patients with amyloidosis presenting to the Massachusetts General Hospital Heart Failure Center or the Boston University School of Medicine/Boston Medical Center Amyloid Treatment and Research Program with New York Heart Association (NYHA) Class III or IV heart failure despite medical therapy. Institutional Review Board approval was obtained to analyze the outcomes of these patients. High-dose chemotherapy/ASCT without a prior OHT was contraindicated in all patients because of severe involvement of the heart by amyloidosis. All patients had the diagnosis of PCD established based on serum and urine electrophoresis with immunofixation studies, measurement of serum-free light-chain concentrations, and bone marrow biopsies. Cardiac amyloidosis was confirmed by endomyocardial biopsy and Congo red staining. Immunohistochemistry of the endomyocardial biopsy specimens was performed to identify the specific type of light chains present, lambda versus kappa. The diagnosis of heart failure was confirmed by right heart catheterization showing increased ventricular filling pressures, a depressed cardiac index, or both. All patients underwent coronary angiography to exclude significant epicardial coronary artery disease. In addition to the routine cardiac transplant evaluation studies, patients also underwent tests to assess the extent and severity of amyloidosis, including upper and lower gastrointestinal endoscopies with biopsies. Patients with hepatic dysfunction or renal dysfunction (defined as serum creatinine ≥2.0, serum alanine/aspartate aminotransferase ≥ twice the upper limit of normal) that persisted after improvement of their hemodynamics (right atrial pressure ≤ 8 mm Hg, cardiac index ≥2.4 L/min m²) underwent liver biopsy, kidney biopsy, or both. Patients who met defining criteria for multiple myeloma (presence of an M-protein in serum or urine, 10% or more clonal bone marrow plasma cells, and related tissue or organ damage including hypercalcemia, renal injury, anemia, or lytic bone lesions) were excluded from further consideration for transplantation. In addition, patients with severe coagulopathy, hepatosplenomegaly, or medication non-compliance were also excluded.

**Cardiac Transplantation**

Patients considered eligible for sequential transplantation were listed as recipients with the Organ Procurement and Transplantation Network (OPTN). Inotropic or mechanical support was used as needed, and waiting list status was determined without consideration of the underlying diagnosis. OHT was performed using the bicaval anastomotic technique, and immunosuppression was administered according to the standard institutional protocol. All patients were discharged from the hospital receiving a calcineurin inhibitor (cyclosporine 4–8 mg/kg per day with a target whole blood trough level of 200–300 ng/mL or tacrolimus 0.15–0.30 mg/kg per day with a target whole blood trough level of 5–15 ng/mL), mycophenolate mofetil (1.0–2.0 g/day), and prednisone (0.4–0.5 mg/kg per day). Follow-up of transplant recipients for allograft rejection was performed by serial right heart catheterization and endomyocardial biopsy (once weekly for 4 weeks, then once every 2 weeks for 8 weeks, then once monthly for 6 months, then once every 2 months for 6–12 months, and then once every 6 months), with tapering of the prednisone dose in the absence of clinically significant rejection.

**Plasma-Cell–Targeted Therapy Before ASCT**

All patients received high-dose melphalan before ASCT for their AL amyloidosis. Only three patients received some form of therapy before OHT: patients 2 and 4 each received one course of melphalan and prednisone (melphalan 10 mg/m² once daily for 4 days with prednisone 100 mg daily for 4 days) and patient 8 received dexamethasone 10 mg daily for 4 days every week over a course of 3 months before OHT.

**Autologous Stem-Cell Transplantation**

Preparation for ASCT was begun when each patient’s prednisone dose was less than or equal to 10 mg/day and they were otherwise clinically stable. Mycophenolate therapy was gradually tapered off, and 2 to 3 weeks later peripheral blood stem cells were collected by leukapheresis after mobilization with granulocyte colony stimulating factor administered at a dose of 5 μg/kg subcutaneously twice daily for 4 days, with apheresis beginning on the 5th day. The intended total target cell dose was more than or equal to 2 × 10⁸ CD34+ cells/kg body weight. Patients were then evaluated based on our institutional ASCT eligibility criteria. High-dose melphalan was administered at a total dose of 140 to 180 mg/m² intravenously over 2 days. Stem cell infusions (day 0) were performed 48 hr after the second dose of melphalan. Supportive care was provided based on our institutional guidelines.

**Follow-Up of Recipients of Cardiac and Stem-Cell Transplants**

Patients were followed up clinically and with serial endomyocardial biopsies. All endomyocardial biopsy specimens were stained with hematoxylin-eosin to assess for allograft rejection, and with Congo red to assess for the presence of amyloid deposits. The presence of birefringence under polarized light was used to confirm the presence of amyloid protein. Specimens with positive Congo red staining then underwent indirect immunofluorescence staining for the presence of amyloid protein. One-year after OHT, and annually thereafter, patients underwent echocardiography, right and left heart catheterization with endomyocardial biopsy, and coronary angiography. Serum protein electrophoresis and urine protein electrophoresis with immunofixation, as well as serum free light chains, were determined at 3, 6, 9, and 12 months after ASCT, and then annually. Bone marrow biopsy was performed (as feasible) between 3 and 12 months after ASCT, then as clinically indicated.
Analysis of Clinical Outcomes

Information regarding patient and cardiac allograft survival and frequency of allograft rejection are available for all patients in the study population and for 17,389 patients undergoing cardiac transplantation for diagnoses other than amyloidosis as registered in the International Society for Heart and Lung Transplantation (ISHLT) database during this time period. Information regarding patient and allograft survival in a cohort of 10 AL amyloidosis patients who received cardiac transplant but not ASCT was kindly provided for comparison by Dr. Jeffrey Hosenpud.

Statistical Analysis

Data are presented as mean±SD or as median (range). Survival curves and survival rates are estimated using Kaplan-Meier method. Comparisons of survival between two groups of patients were made using the log-rank and Wilcoxon tests. Statistical significance is determined by a P value less than 0.05. We used SAS Version 9 for statistical analyses.

RESULTS

Between September 2000 and January 2008, 26 patients with systemic amyloidosis unable to undergo ASCT due to severe heart failure presented to the Massachusetts General Hospital Heart Failure Center for further evaluation. On completion of the evaluation, 18 patients were listed with the OPTN as potential heart recipients; eight patients were excluded due to a significant contraindication to OHT or ASCT (Fig. 1). Nine of the transplanted candidates subsequently underwent OHT, whereas nine eligible patients died prior to transplantation (DPT) due to the lack of a cardiac donor. Of the nine patients who underwent cardiac transplantation, eight patients underwent ASCT. Because of poor performance status for a prolonged period of time after OHT, one patient did not proceed to ASCT and shortly thereafter died from progressive amyloidosis.

Patient Characteristics

The characteristics of the patients listed for transplantation are shown in Table 1. Three patients in the OHT group were found to have coronary artery disease and underwent percutaneous intervention before their transplant, whereas no patients in the DPT were found to have coronary artery disease. All patients were NYHA functional class III or IV.

![FIGURE 1. Summary of the treatment allocation scheme.](image)

**TABLE 1. Characteristics of patients listed as potential sequential heart and ASCT candidates**

<table>
<thead>
<tr>
<th></th>
<th>OHT, n=9</th>
<th>Died before OHT, n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) (yr)</td>
<td>57 (38–67)</td>
<td>54 (42–64)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 7, female 2</td>
<td>Male 5, female 4</td>
</tr>
<tr>
<td>Symptom onset to diagnosis, median (mo)</td>
<td>14 (3–26)</td>
<td>7 (1–24)</td>
</tr>
<tr>
<td>Diagnosis to conclusion of OHT evaluation (mo)</td>
<td>5.4 (2.4–10)</td>
<td>6.2 (1–14)</td>
</tr>
<tr>
<td>NYHA class III, IV at evaluation</td>
<td>3, 6</td>
<td>2, 7</td>
</tr>
<tr>
<td>Type of light chain</td>
<td>λ 7, κ 2</td>
<td>λ 7, κ 2</td>
</tr>
<tr>
<td>LVEF%</td>
<td>37±4</td>
<td>46±4</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>13±1</td>
<td>14±1</td>
</tr>
<tr>
<td>LV end-diastolic internal dimension (mm)</td>
<td>41±4</td>
<td>46±4</td>
</tr>
<tr>
<td>Mechanical circulatory support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>BiVAD</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>IABP</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Renal involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein excretion (mg/24 hr)</td>
<td>279±114</td>
<td>569±79</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>53±6</td>
<td>47±4</td>
</tr>
<tr>
<td>Kidney biopsy</td>
<td>2, positive for amyloid</td>
<td>3, positive for amyloid</td>
</tr>
<tr>
<td>Gastrointestinal/liver involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms/gastroparesis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal biopsies</td>
<td>8, positive for amyloid</td>
<td>9, positive for amyloid</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>2, positive for amyloid</td>
<td>1, positive for amyloid</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

AsCT, autologous stem-cell transplantation; OHT, orthotopic heart transplantation; LVEF, left ventricular ejection fraction; LV, left ventricular; LVAD, left ventricular assist device; BiVAD, biventricular assist device; IABP, intraaortic balloon pump.

Patients who underwent successful cardiac transplantation had a longer period of time from the onset of symptoms to diagnosis (14 vs. 7 months, P<0.05), but a similar duration from diagnosis to listing as a cardiac transplant recipient with the OPTN. Echocardiographic assessment of cardiac function showed a left ventricular (LV) ejection fraction of less than 50% in all patients except one in each group. All patients had abnormal LV wall thickness (>11 mm) in the presence of a normal LV internal dimension (<54 mm). Seven patients in the OHT group had lambda subtype AL amyloidosis and two had kappa AL amyloidosis; this was a similar distribution to that seen in the DPT group. Monoclonal plasma cells comprised 5% to 10% of marrow cellularity in both groups, with no significant difference between the OHT and DPT groups. Extracardiac solid organ involvement by amyloidosis was
present in all patients. At the time of evaluation, significant proteinuria was present in two of the OHT patients and in five of the DPT patients. OHT patients had, on average, less proteinuria than DPT patients, but creatinine clearance was similar between the two groups (Table 1). Renal biopsies were performed in two patients in the OHT group and in three patients in the DPT group. Evidence of amyloid deposition was seen in all five of these patients.

All patients underwent esophagogastroduodenoscopy and colonoscopy with biopsy as part of their evaluation, and all but one of the patients had evidence of amyloid deposition in the gastrointestinal tract. Two patients had early satiety due to gastroparesis, which was confirmed by radionuclide gastric emptying studies. In one of these patients, severe malnutrition developed, leading to removal from the donor waiting list. Two patients in the OHT group and one in the DPT group underwent liver biopsies for persistently abnormal serum transaminases and bilirubin, all three with biopsies positive for amyloid deposition. However, right atrial pressure was also increased in all these patients, and their abnormal hepatic function tests all resolved after cardiac transplantation.

**Circulatory Support Before Transplantation**

While awaiting cardiac transplantation, all patients required mechanical circulatory support (Table 1) or intravenous inotropic support. At the time of transplantation, three of the OHT patients required mechanical circulatory support; two with left ventricular assist devices and one with a biventricular assist device. The other six OHT patients received dobutamine, with two patients also requiring milrinone to maintain adequate cardiac output. The one patient in the DPT group who died with biventricular assist device support developed refractory hypercalcemia due to progression to multiple myeloma and renal failure.

**Cardiac Transplantation**

OHT was performed in all patients using the bicaval anastomotic technique. Because of significant renal impairment, patient 4 received a kidney allograft along with the cardiac allograft. Two patients required early re-exploration for bleeding within the first 48 hr postoperatively. OHT patients required intensive care for a median of 8.5 days (range, 6–30 days) and were discharged from the hospital 22±3 days after surgery. Three OHT patients received cytolytic induction therapy due to the development of transient renal dysfunction; two with monoclonal murine anti-CD3 antibodies and one with antithymocyte globulin. All patients were discharged on a calcineurin inhibitor, mycophenolate mofetil, and prednisone. Patient 6 was hospitalized for congestive heart failure within a month of his OHT and a biopsy demonstrated myocardial necrosis consistent with ischemic injury, without signs of rejection. Echocardiogram showed an LV ejection fraction of 24% with extensive anterior septal wall motion abnormalities, and subsequent coronary angiography revealed complete occlusion of the proximal left anterior descending coronary artery. Despite urgent coronary intervention, the patient required support with an intraaortic balloon pump and subsequently received a second OHT.

**Autologous Stem-Cell Transplantation**

The median time interval between heart transplantation and stem-cell transplantation was 7.0 months. In one patient, ASCT was delayed until 11 months after OHT because of the occurrence of grade 3A cardiac allograft rejection 5 months after transplantation that required augmentation of immunosuppression. Stem-cell procurement in all patients was successful after mobilization with granulocyte colony-stimulating factor (G-CSF), with a yield of more than or equal to 2×10⁹ CD34+ cells/kg in each patient (median 3.47×10⁹/kg; range 2.3–3.97×10⁹/kg). G-CSF was tolerated well by all except patient 5 who developed “fluid retention syndrome” during leukapheresis, manifested by significant weight gain, pleural effusions, and lower extremity edema which were all successfully treated with diuretics. Neutrophil and platelet engraftment (absolute neutrophil count >0.5×10⁹/L, platelet count >20×10⁹/L) was achieved approximately 12 days after stem-cell infusion in all patients except patient 7, who died from overwhelming *Escherichia coli* sepsis 8 days after ASCT. Three patients who were cytomegalovirus seropositive before OHT had reactivation of infection after stem-cell transplantation as indicated by a positive cytomegalovirus antigenemia assay. All three were successfully treated with ganciclovir followed by valganciclovir.

**Hematologic Responses**

Disease characteristics and response to treatment in seven evaluable patients who received OHT followed by ASCT are summarized in Table 2. At day +100 post-ASCT, six of the seven patients (85%) achieved a complete hematologic remission (CR) and one patient (patient 5) achieved a partial remission. Two of the six patients (patients 3 and 4) who achieved CR later developed evidence of PCD at 18 and 52 months, respectively, after ASCT, with the other four patients remaining in hematologic CR.

**Clinical Outcome**

Follow-up information is available for all eight of the OHT/ASCT patients at a median of 56 months (range, 12–101 months post-OHT). Transplant-related mortality has been 12.5% and overall mortality has been 37.5%, with one patient dying from overwhelming sepsis within a month of ASCT, one from progressive amyloidosis 35 months after OHT, and one from sudden cardiac death 45 months after OHT. At a median follow-up of 56 months, median overall or disease-free survival by Kaplan-Meier estimate was not reached (Figs. 2 and 3). Five of eight patients (62.5%) are alive with a good functional status (NYHA class 1) and no signs of recurrent amyloidosis, 49 to 101 months from the time of cardiac transplantation. These five patients remain on therapeutic doses of cyclosporine or tacrolimus, mycophenolate mofetil, and low-dose prednisone (5–10 mg/day). Four patients have no evidence of recurrent PCD. Two of our patients developed recurrent amyloidosis as evidenced by increased plasma light-chain concentrations, increased marrow plasmacytosis, and clinical signs of amyloidosis. Patient 3 had an increase in plasma light chain concentration and relapse of marrow plasmacytosis 18 months after stem-cell transplantation. This patient also developed allograft coronary vasculopathy, but endomyocardial biopsy
was negative for amyloid. She died suddenly 45 months after OHT. Patient 5, who achieved only a partial remission after ASCT, was noted to have an increasing plasmacytosis (5%) in her bone marrow 12 months after ASCT, along with a slowly increasing serum paraproteinemia and lambda-free light-chain concentration. She later presented with clinical evidence of systemic amyloidosis and did not respond to thalidomide and dexamethasone. Amyloid deposition was identified on a subsequent endomyocardial biopsy, and the patient eventually died from progressive cardiac, liver, and

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Time: Dx to OHT (mo)</th>
<th>Time: OHT to ASCT (mo)</th>
<th>Therapy pre-OHT</th>
<th>Status of remission at day 100 post-ASCT</th>
<th>Recurrence of plasma cell dyscrasia (mos after ASCT)</th>
<th>Recurrent amyloidosis (mos after ASCT)</th>
<th>Endomyocardial biopsies for amyloid (mos after ASCT)</th>
<th>Current status (mo after OHT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 61/M</td>
<td>3</td>
<td>9</td>
<td>No</td>
<td>CR</td>
<td>No</td>
<td>No</td>
<td>Negative</td>
<td>Alive and well (101)</td>
</tr>
<tr>
<td>2 58/M</td>
<td>10</td>
<td>8</td>
<td>Yes (MP)</td>
<td>CR</td>
<td>No</td>
<td>No</td>
<td>Negative</td>
<td>Alive and well (77)</td>
</tr>
<tr>
<td>3 55/F</td>
<td>5</td>
<td>11</td>
<td>No</td>
<td>CR</td>
<td>Yes (18)</td>
<td>? ecchymosis gastroparesis (28)</td>
<td>Negative</td>
<td>Sudden death (45)</td>
</tr>
<tr>
<td>4 67/M</td>
<td>8</td>
<td>7</td>
<td>Yes (MP)</td>
<td>CR</td>
<td>Yes (50)</td>
<td>No</td>
<td>Negative</td>
<td>Alive and well (65)</td>
</tr>
<tr>
<td>5 38/F</td>
<td>8</td>
<td>4</td>
<td>No</td>
<td>PR</td>
<td>Yes (11)</td>
<td>Yes, hepatomegaly, biopsy positive (20)</td>
<td>Positive (20)</td>
<td>Died (35)</td>
</tr>
<tr>
<td>6 45/M</td>
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<td>7</td>
<td>No</td>
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<td>No</td>
<td>No</td>
<td>Negative</td>
<td>Alive and well (49)</td>
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<tr>
<td>7 54/M</td>
<td>14</td>
<td>6</td>
<td>No</td>
<td>CR</td>
<td>No</td>
<td>No</td>
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<tr>
<td>8 57/M</td>
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<td>7</td>
<td>Dex</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>Negative</td>
<td>Died (7)</td>
</tr>
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</table>

* Median 7 mo.

** Median 7 mo.

MP, melphalan and prednisone; Dex, dexamethasone; CR, complete remission; PR, partial remission; OHT, orthotopic heart transplantation; ASCT, autologous stem-cell transplantation.

FIGURE 2. Kaplan-Meier overall survival estimates, according to treatment. Open circles represent patients whose data were censored at the last time they were known to be alive. Comparisons of survival between two groups of patients were made using the log-rank and Wilcoxon tests. OHT, orthotopic heart transplant; ASCT, autologous hematopoietic stem-cell transplant; ISHLT, International Society for Heart and Lung Transplantation.
renal failure 35 months after OHT. Patient 4 has recently been found to have recurrent PCD based on recurrence of a mono-
clonal gammopathy and a monoclonal plasmacytosis in the bone marrow at 52 months after ASCT, but he has had no clinical signs of amyloidosis and a recent endomyocardial biopsy was negative for amyloid. Serial endomyocardial biopsies after both OHT and ASCT have shown evidence of recurrent amyloid in the cardiac allograft of only one patient (patient 5).

**DISCUSSION**

Five of our eight patients who underwent sequential OHT/ASCT are alive with a good functional status (NYHA class I) at a median follow-up of 56 months (range, 7–101 months). None have evidence of recurrent amyloidosis, with four remaining in complete hematologic remission. The actuarial survival of these patients (Fig. 2) is 60% at 7 years, which is not significantly different from the outcomes of 17,389 patients collected in the database of the ISHLT who underwent OHT for nonamyloid heart disease during the same time. This is in contrast to the previously reported overall survival of 39% at 4 years in 10 patients with AL amyloidosis who received a cardiac transplant without ASCT (13). Gilmore et al. recently reported sequential OHT/ASCT in five patients with AL cardiac amyloidosis. Two died from progressive amyloidosis and three are alive, including one who developed progressive PCD that was successfully treated with high-dose corticosteroids (17). Lacy et al. from the Mayo Clinic have also published a series of 11 patients undergoing sequential OHT/ASCT. They reported a 5-year overall survival rate of 62%, but overall survival was only 25% at 8 years. Two patients died from transplant-related toxicity and three died from progressive amyloidosis (18). In contrast, the actuarial disease-free survival (without recurrent amyloidosis) in our patients at 8 years is 60%. The factors responsible for this possible improvement may include patient selection (less severe systemic amyloidosis) and improvements in supportive care post-ASCT.

Although these small series included only carefully selected patients, the results indicate that good outcomes are achievable in patients with severe cardiac AL amyloidosis after OHT if their PCD is successfully treated afterward. This is a significant step forward from the outcomes of the 10 pa-
tients in Hosenpud’s study who received OHT without subse-
quent ASCT, the majority of whom developed progressive amyloidosis involving major organs and recurrent amyloid deposition in their cardiac allografts.

The PCD relapsed in three of our seven evaluable pa-
tients 12 to 52 months after ASCT, but only one patient (pa-
tient 5) had biopsy-proven evidence of amyloid in the cardiac allograft. This is the only patient who had clinically significant fluid retention syndrome during the stem-cell mobilization and after ASCT, and she eventually died from progressive amyloidosis complicated by multiorgan failure. Of note, patients with fluid retention syndrome are being increasingly recognized to have a particularly poor prognosis (19). Interestingly, amyloid deposition in the transplanted heart of this patient was believed to have had little, if any, clinical significance; there was no echocardiographic evidence of amyloid cardiomyopa-thy. In contrast to our experience, five of 11 patients reported by Lacy et al. showed amyloid deposition in the cardiac allograft, although none of them had symptoms, echocardiographic evidence, or biochemical evidence of cardiac amyloidosis (18). A similar observation was reported by Hosenpud et al. where the majority of patients undergoing OHT without subsequent ASCT died from progressive disease involving the major organs and had recurrent amyloid deposition in the allograft, but cardiac amyloidosis had no apparent clinical significance (13). In contrast, Gilmore showed that relapse of the PCD after ASCT was associated with characteristic echocardiographic evidence of cardiac amyloidosis and rise in serum NT-pro-BNP (17). Although conclusions are limited by the small sample size in our study, the observation of a lack of clinically significant recurrent amyloidosis in the transplanted heart despite the presence of clear disease progression in other organs might be due to an “altered” amyloidogenic property of light chains with particular respect to the “allogeneic” heart. It is possible that, in time, additional patients will demonstrate clinical manifestations of cardiac amyloidosis if light chain production is not ade-
quately controlled.

Unfortunately, patients with AL amyloidosis and severe heart failure have an extraordinarily poor prognosis on com-
pleting their cardiac transplant evaluation. Of 26 patients evaluated, 18 patients were carefully selected and listed with the OPTN for OHT/ASCT, but only half survived to OHT.
Nine patients died while waiting for OHT (DPT group) due to cardiac causes or other complications of systemic amyloidosis, and one patient had progression to multiple myeloma. With regard to patient characteristics, there were no significant differences between the patients who received sequential OHT/ASCT and the patients who did not (DPT). However, the patients in the former group had a significant improvement in their clinical outcomes after OHT/ASCT, and this increases the possible need for a change in cardiac donor allocation. The earlier application of plasma-cell-targeted therapeutic approaches with newer agents, such as bortezomib and lenalidomide (16, 20), which are effective and better tolerated than conventional chemotherapeutics, beginning at the time of the evaluation process may be beneficial, and improve patients’ chances for receiving an OHT. A similar approach may also be considered for patients who are not ready for ASCT after OHT since a prolonged time without treatment may allow progression of the amyloidosis and therefore both impair the candidacy of these patients for ASCT and increase their transplant-related mortality.

Our observation of a similar survival in patients with amyloid heart disease undergoing sequential heart and stem-cell transplant to those in the ISHLT registry undergoing heart transplant for other diagnoses is subject to several limitations. Survival after cardiac transplantation has continued to improve in patients with advanced heart failure due to causes other than amyloidosis. We have observed recurrent plasma-cell disease in several of our patients after sequential heart and stem-cell transplantation that may limit their future survival. Thus, it is possible that survival in the two groups of patients beyond the time described may differ.

In conclusion, the tandem approach of OHT followed by high-dose melphalan and ASCT is a feasible strategy and can improve the survival of carefully selected patients with systemic AL amyloidosis who present with overt heart failure. A multidisciplinary approach dedicated to early diagnosis, appropriate and timely screening for OHT/ASCT, and a multimodality PCD-specific strategy incorporating both high-dose melphalan/ASCT and nontransplant steps (before OHT, after OHT, and after ASCT) is currently underway at the MGH to address AL amyloidosis patients who present with severe cardiac amyloidosis.

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