Published in final edited form as:

Transplantation. 2010 October 27; 90(8): 905–911. doi:10.1097/TP.0b013e3181f10edb.

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

Bimalangshu R Dey, MD, PhD.¹, Stephen S Chung, MD¹, Thomas R Spitzer, MD¹, Hui Zheng, PhD.², Thomas E. MacGillivray, MD³, David C Seldin, MD, PhD.* , Steven McAfee, MD¹, Karen Ballen, MD¹, Eyal Attar, MD¹, Thomas Wang, MD⁴, Jordan Shin, MD⁴, Christopher Newton-Cheh, MD, MPH⁴, Stephanie Moore, MD⁴, Vaishali Sanchorawala, MD*, Martha Skinner, MD*, Joren C. Madsen, MD, DPhil³, and Marc J. Semigran, MD.⁴

¹ Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA

² Biostatistics Center, Massachusetts General Hospital, Boston, MA, USA

³ Cardiac Surgery, Massachusetts General Hospital, Boston, MA, USA

⁴ Cardiology, Massachusetts General Hospital, Boston, MA

* Stem Cell Transplantation and Amyloid Treatment and Research Programs, Department of Medicine, Boston University School of Medicine and Boston Medical Center, Boston MA

Abstract

Background—Patients with AL amyloidosis who present with severe heart failure due to cardiac involvement rarely survive more than six 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.

Corresponding Author: Marc J. Semigran MD, Bigelow 800, Massachusetts General Hospital, Fruit St., Boston, MA 02114, 617-726-8862, msemigran@partners.org.

AUTHORS' CONTRIBUTIONS:

Bimalangshu R Dey- Writing and editing of manuscript, collection of and analysis of data, direct care of patients undergoing bone marrow transplantation.

Stephen S Chung- Writing and editing of manuscript, collection of and analysis of data.

Thomas R Spitzer- Direct care of patients undergoing bone marrow transplantation.

Hui Zheng- Statistical analysis of data.

Thomas E MacGillivray- Direct care of patients undergoing orthotopic heart transplantation.

David C Seldin- Initial diagnosis of and direct care of patients who presented to Boston Medical Center.

Steven McAfee- Direct care of patients undergoing bone marrow transplantation.

Karen Ballen- Direct care of patients undergoing bone marrow transplantation.

Eyal Attar- Direct care of patients undergoing bone marrow transplantation.

Thomas Wang- Direct care of and management of heart failure in our patients

Jordan Shin- Direct care of and management of heart failure in our patients.

Christopher Newton-Cheh- Direct care of and management of heart failure in our patients.

Stephanie Moore- Direct care of and management of heart failure in our patients.

Vaishali Sanchorawala- Initial diagnosis of and direct care of patients who presented to Boston Medical Center.

Martha Skinner- Initial diagnosis of and direct care of patients who presented to Boston Medical Center.

Joren C Madsen- Direct care of patients undergoing orthotopic heart transplantation.

Marc Semigran- Writing and editing of manuscript and the revision, collection of and analysis of data, direct care of and management of heart failure in our patients.

All of the above authors have read the manuscript and provided critical review.

CONFLICT OF INTEREST STATEMENT: There are no conflicts of interest for the authors to disclose.

Methods—We developed a treatment strategy of cardiac transplant followed by ASCT. 26 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 to 17,389 patients who received heart transplants for non-amyloid heart disease: 64% in *non-amyloid* vs. 60% in *amyloid* patients at seven 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. (clinicaltrials.gov, NCT00456040)

Keywords

Amyloid; Cardiac Amyloidosis; Stem Cell Transplantation

INTRODUCTION

Systemic AL amyloidosis is a plasma cell dyscrasia marked by the progressive systemic deposition of monoclonal immunoglobulin light chains as amyloid fibrils leading to organ failure and death¹⁸. 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 a particularly poor prognosis, with a median survival of only 6 months and a 100% mortality at two years^{1,3,8,9,19}. 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, 10} and, therefore, are currently precluded from undergoing ASCT at most centers.

In 1988 cardiac transplantation began to be used to treat AL amyloidosis patients with overt heart failure¹¹. 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^{11–14}. Hosenpud, et al., reported a 4-year survival rate of 39% in these cardiac transplant recipients, with significant systemic progression of amyloidosis in the majority.¹² 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 non-amyloid causes¹³. Based on these discouraging outcomes and the shortage of donor organs, amyloid heart disease has been considered a contraindication for OHT.

In 2004 Skinner, et al., reported a complete hematologic response, defined as no evidence of an underlying plasma cell dyscrasia one year after treatment, in 40% of patients with primary AL amyloidosis who received high-dose melphalan followed by ASCT⁵. This raised the possibility of achieving long-term survival without progressive amyloid deposition, if amyloid patients undergoing cardiac transplantation were subsequently given high-dose chemotherapy and ASCT²². 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^{15, 16}.

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 paper we report the outcomes of 26 patients with AL amyloidosis complicated by severe heart failure referred to the MGH for sequential cardiac transplantation and dose-intensive melphalan and ASCT.

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 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 orthotopic heart transplantation (OHT) was contraindicated in all patients because of severe involvement of the heart by amyloidosis. All patients had the diagnosis of plasma cell dyscrasia (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 elevated 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 $\geq$ twice the upper limit of normal) that persisted after improvement of their hemodynamics (right atrial pressure ≤ 8 mmHg, 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, ten percent 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 noncompliance 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 utilized as needed, and waiting list status was determined without consideration of the underlying diagnosis.

OHT was performed using the bicaval anastomatic 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/day with a target whole blood trough level of 200–300 ng/ml or tacrolimus 0.15–0.30 mg/kg/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/day). Follow-up of transplant recipients for allograft rejection was performed by serial right heart catheterization and endomyocardial biopsy (once weekly $\times 4$ wks, then once every 2 wks $\times 8$ wks, then once monthly $\times 6$ months, then once every 2 months $\times 6$ –12 months, then once every 6 months), with tapering of the prednisone dose in the absence of clinically significant rejection.

Plasma cell –targeted therapy prior to ASCT

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

Autologous Stem Cell Transplantation

Preparation for ASCT was begun when each patient's prednisone dose was ≤ 10 mg/day and they were otherwise clinically stable. Mycophenolate therapy was gradually tapered off, and 2–3 weeks later peripheral blood stem cells (PBSC) were collected by leukapheresis after mobilization with granulocyte colony stimulating factor (GCSF) administered at a dose of 5 mcg/kg subcutaneously twice daily for 4 days, with apheresis beginning on the 5th day. The intended total target cell dose was $\geq 2 \times 10^6$ CD34+ cells/kg body weight. Patients were then evaluated based on our institutional autologous stem cell transplant eligibility criteria. High-dose melphalan was administered at a total dose of 140–180 mg/m² intravenously over two days. Stem cell infusions (day 0) were performed 48 hours 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 clinically and with serial endomyocardial biopsies. All endomyocardial biopsy specimens were stained with hematoxylin and 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 (SPEP) and Urine protein electrophoresis (UPEP) with immunofixation (IF), as well as serum free light chains, were determined at 3, 6, 9, 12 months following ASCT, then annually. Bone marrow biopsy was performed (as feasible) between 3 and 12 months following ASCT, then as clinically indicated.

Analysis of Clinical Outcomes

Information regarding patient and cardiac allograft survival and frequency of allograft rejection is 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 $\pm$ 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. Upon completion of the evaluation, 18 patients were listed with the Organ Procurement and Transplant Network (OPTN) as potential heart recipients; eight patients were excluded due to a significant contraindication to either OHT or ASCT (Figure 1). Nine of the transplant candidates subsequently underwent OHT, while 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 following 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 prior to their transplant, while no patients who DPT were found to have coronary artery disease. All patients were NYHA functional class III or IV. 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 $< 50\%$ 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 5–10% 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 GI 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 elevated in all of these patients, and their abnormal hepatic function tests all resolved after cardiac transplantation.

Circulatory support prior to transplantation

While awaiting cardiac transplantation, all patients required either mechanical circulatory support (MCS) (Table 1) or intravenous inotropic support. At the time of transplantation, three of the OHT patients required MCS, two with left ventricular assist devices (LVAD), and one with a biventricular assist device (BiVAD). 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 BiVAD 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 hours postoperatively. OHT patients required intensive care for a median of 8.5 days (range 6–30), and were discharged from the hospital 22 ± 3 days after surgery. Three of the 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 LVEF 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, he 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 five months after transplantation that required augmentation of immunosuppression. Stem cell procurement in all patients was successful following mobilization with G-CSF, with a yield of $\geq 2 \times 10^6$ CD34+ cells/kg in each patient (median 3.47×10^6 /kg; range $2.3 - 3.97 \times 10^6$ /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 $> 0.5 \times 10^9$ /L, platelet count $> 20 \times 10^9$ /L) was achieved approximately 12 days after stem cell infusion in all patients except patient #7, who died from overwhelming *E coli* sepsis eight days following ASCT. Three patients that were cytomegalovirus (CMV) seropositive before OHT had reactivation of infection after stem cell transplantation as indicated by a positive CMV 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 out of seven patients (85%) achieved a complete hematologic remission (CR)¹⁰ and one patient (patient #5) achieved a partial remission (PR). Two of the six patients (patients #3, #4) who achieved CR later developed evidence of plasma cell dyscrasia (PCD) at 18 and 52 months, respectively, following 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 following OHT. At a median follow-up of 56 months,

median overall or disease-free survival by Kaplan-Meier estimate were not reached (Figures 2 & 3). Five out of eight patients (62.5%) are alive with a good functional status (NYHA Class I) 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 daily). Four patients have no evidence of recurrent plasma cell dyscrasia (PCD).

Two of our patients developed recurrent amyloidosis as evidenced by elevated 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 following 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 renal failure 35 months after OHT. Patient #4 has recently been found to have recurrent PCD based on recurrence of a monoclonal gammopathy and a monoclonal plasmacytosis in the bone marrow at 52 months following ASCT, but he has had no clinical signs of amyloidosis and a recent endomyocardial biopsy was negative for amyloid. Serial endomyocardial biopsies following 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 to 101 months). None have evidence of recurrent amyloidosis, with four remaining in complete hematologic remission. The actuarial survival of these patients (Figure 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 non-amyloid 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 ASCT¹². 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 corticosteroids¹⁵. Lacy and colleagues 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 amyloidosis¹⁶. 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 following OHT if their PCD is successfully treated afterwards. This is a significant step forward from the outcomes of the ten patients in Hosenpud's study who received OHT without subsequent ASCT, the majority of whom developed progressive amyloidosis involving major organs and recurrent amyloid deposition in their cardiac allografts.

The plasma cell dyscrasia relapsed in three of our seven evaluable patients 12 to 52 months following ASCT, but only one patient (patient #5) had biopsy-proven evidence of amyloid in the cardiac allograft. This is the only patient who had clinically significant fluid retention during the stem cell mobilization and after ASCT, and she eventually died from progressive amyloidosis complicated by multi-organ failure. Of note, patients with fluid retention syndrome are being increasingly recognized to have a particularly poor prognosis²⁰. 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 cardiomyopathy. In contrast to our experience, five out of eleven patients reported by Lacy et al. showed amyloid deposition in the cardiac allograft, though none of them had symptoms, echocardiographic evidence, or biochemical evidence of cardiac amyloidosis¹⁶. 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 significance¹². Gilmore, in contrast, showed that relapse of the plasma cell dyscrasia following ASCT was associated with characteristic echocardiographic evidence of cardiac amyloidosis and rise in serum NT-pro-BNP¹⁵. While 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 adequately controlled.

Unfortunately, patients with AL amyloidosis and severe heart failure have an extraordinarily poor prognosis upon completing their cardiac transplant evaluation. Out 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) either due to cardiac causes or other complications of systemic amyloidosis; one patient had progression to multiple myeloma. With regards 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 following OHT/ASCT, and this raises 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^{21,22}, 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 non-transplant steps (prior to OHT, after OHT, and following ASCT) is currently underway at the MGH to address AL amyloidosis patients who present with severe cardiac amyloidosis.

Acknowledgments

Amyloid research at Boston University School of Medicine/Boston Medical Center was supported by grants from the National Institutes of Health (P01 HL68705), the Gerry Foundation, and the Amyloid Research Fund at Boston University. These funding sources had no influence on the study design, the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Abbreviations

ASCT	Autologous stem cell transplantation
OHT	Orthotopic heart transplantation
PCD	Plasma cell dyscrasia
SPEP	Serum protein electrophoresis
UPEP	Urine protein electrophoresis
IF	Immunofixation
ISHLT	International Society for Heart and Lung Transplantation
DPT	Died prior to transplant

References

1. Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med.* 1996; 100:290–8. [PubMed: 8629674]
2. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med.* 1997; 336:1202–7. [PubMed: 9110907]
3. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol.* 1995; 32:45–59. [PubMed: 7878478]
4. Gertz MA, Lacy MQ, Lust JA, Greipp PR, Witzig TE, Kyle RA. Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis. *J Clin Oncol.* 1999; 17:262–7. [PubMed: 10458241]
5. Skinner M, Sanchawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med.* 2004; 140:85–93. [PubMed: 14734330]
6. Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. *Bone Marrow Transplant.* 2004; 34:1025–31. [PubMed: 15516945]
7. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. *Blood.* 2004; 103:3960–3. [PubMed: 14739213]
8. Gertz MA, Kyle RA, Greipp PR. Response rates and survival in primary systemic amyloidosis. *Blood.* 1991; 77:257–62. [PubMed: 1985692]

9. Dubrey SW, Cha K, Anderson J, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. *QJM*. 1998; 91:141–57. [PubMed: 9578896]
10. Saba N, Sutton D, Ross H, et al. High treatment-related mortality in cardiac amyloid patients undergoing autologous stem cell transplant. *Bone Marrow Transplant*. 1999; 24:853–5. [PubMed: 10516696]
11. Conner R, Hosenpud JD, Norman DJ, Pantely GA, Cobanoglu A, Starr A. Heart transplantation for cardiac amyloidosis: successful one-year outcome despite recurrence of the disease. *J Heart Transplant*. 1988; 7:165–7. [PubMed: 3284989]
12. Hosenpud JD, DeMarco T, Frazier OH, et al. Progression of systemic disease and reduced long-term survival in patients with cardiac amyloidosis undergoing heart transplantation. Follow-up results of a multicenter survey. *Circulation*. 1991; 84:III338–43. [PubMed: 1934428]
13. Dubrey SW, Burke MM, Hawkins PN, Banner NR. Cardiac transplantation for amyloid heart disease: the United Kingdom experience. *J Heart Lung Transplant*. 2004; 23:1142–53. [PubMed: 15477107]
14. Kpodonu J, Massad MG, Caines A, Geha AS. Outcome of heart transplantation in patients with amyloid cardiomyopathy. *J Heart Lung Transplant*. 2005; 24:1763–5. [PubMed: 16297778]
15. Gillmore JD, Goodman HJ, Lachmann HJ, et al. Sequential heart and autologous stem cell transplantation for systemic AL amyloidosis. *Blood*. 2006; 107:1227–9. [PubMed: 16210334]
16. Lacy MQ, Dispenzieri A, Hayman SR, et al. Autologous stem cell transplant after heart transplant for light chain (AL) amyloid cardiomyopathy. *J Heart Lung Transplant*. 2008; 27:823–9. [PubMed: 18656793]
17. Palladini G, Lavatelli F, Russo P, et al. Circulating amyloidogenic free light chains and serum N-terminal natriuretic peptide type B decrease simultaneously in association with improvement of survival in AL. *Blood*. 2006; 107:3854–8. [PubMed: 16434487]
18. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation*. 2005; 112:2047–60. [PubMed: 16186440]
19. Hosenpud JD. Restrictive Cardiomyopathy. *Progress in Cardiology*. 1989:91–105.
20. Burzynski JA, Dispenzieri A, Gertz MA, Lacy MQ, Hoskin TL, Wolf RC. Fluid-Related Complications in Patients with Amyloidosis Associated with Filgrastim during Peripheral Blood Stem Cell Mobilization. *ASH Annual Meeting Abstracts*. 2004; 104:1143.
21. Kastiris E, Anagnostopoulos A, Roussou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. *Haematologica*. 2007; 92:1351–8. [PubMed: 18024372]
22. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. *Blood*. 2007; 110:3561–3. [PubMed: 17673601]
23. Lachmann HJ, Gallimore R, Gillmore JD, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. *Br J Haematol*. 2003; 122:78–84. [PubMed: 12823348]
24. Sanchorawala V, Seldin DC, Magnani B, Skinner M, Wright DG. Serum free light-chain responses after high-dose intravenous melphalan and autologous stem cell transplantation for AL (primary) amyloidosis. *Bone Marrow Transplant*. 2005; 36:597–600. [PubMed: 16044137]
25. Dispenzieri A, Lacy MQ, Katzmann JA, et al. Absolute values of immunoglobulin free light chains are prognostic in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. *Blood*. 2006; 107:3378–83. [PubMed: 16397135]

Figure 1.

Summary of the Treatment Allocation Scheme.

OHT, orthotopic heart transplant; ASCT, autologous hematopoietic stem cell transplant.

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. OHT, orthotopic heart transplant; ASCT, autologous hematopoietic stem cell transplant; ISHLT, International Society for Heart and Lung Transplantation. Comparisons of survival between two groups of patients were made using the log-rank and Wilcoxon tests.

Disease-free Survival of Transplant Recipients

Figure 3.

Kaplan-Meier Disease-Free Survival Estimates, According to Treatment.

MGH, orthotopic heart transplant followed by hematopoietic stem cell transplant for cardiac amyloidosis; Hosenpud, orthotopic heart transplant alone for cardiac amyloidosis.

Comparisons of survival between two groups of patients were made using the log-rank and Wilcoxon tests.

Table 1

Characteristics of Patients Listed as Potential Sequential Heart and ASCT candidates.

	OHT, n=9	Died prior to OHT, n=9
Age, median (range)	57 (38–67) years	54 (42–64) years
Gender	Male 7, Female 2	Male 5, Female 4
Symptom onset to diagnosis, median	14 (3–26) months	7 (1–24) months
Diagnosis to conclusion of OHT evaluation	5.4(2.4–10) months	6.2(1–14) months
NYHA Class III, IV at evaluation	3,6	2,7
Type of light chain	λ 7, κ 2	λ 7, κ 2
LVEF%	37 $\pm$ 4	46 $\pm$ 4
LV wall thickness (mm)	13 $\pm$ 1	14 $\pm$ 1
LV end-diastolic internal dimension (mm)	41 $\pm$ 4	46 $\pm$ 4
Mechanical circulatory support		
LVAD	2	
BiVAD	1	1
IABP		2
Renal Involvement		
Protein excretion (mg/24 hours)	279 $\pm$ 114	569 $\pm$ 79
Creatinine clearance (ml/min)	53 $\pm$ 6	47 $\pm$ 4
Kidney biopsy	2, positive for amyloid	3, positive for amyloid
Gastrointestinal/Liver Involvement		
Symptoms/gastroparesis	1	1
Gastrointestinal biopsies	8, positive for amyloid	9, positive for amyloid
Abnormal liver function	3	4
Liver biopsy	2, positive for amyloid	1, positive for amyloid
Peripheral neuropathy	3	4

Table 2

Outcomes Following Sequential OHT and ASCT.

	Age/sex	Time: Dx To OHT, * months	Time: OHT to ASCT, ** months	Therapy Pre-OHT	Status of Remission at day 100 post-ASCT	Recurrence of plasma cell dyscrasia (mos after ASCT)	Recurrent amyloidosis (mos after ASCT)	Serial cardiac biopsies (amyloid)	Current status; (months after OHT)
1	61/M	3	9	No	CR	No	No	negative	Alive and well (101)
2	58/M	10	8	Yes (MP)	CR	No	No	negative	Alive and well (77)
3	55/F	5	11	No	CR	Yes (18)	? echymosis Gastroparesis (28)	negative	Sudden death (45)
4	67/M	8	7	Yes (MP)	CR	Yes (50)	No	negative	Alive and well (65)
5	38/F	8	4	No	PR	Yes (11)	Yes, hepatomegaly, biopsy positive (20)	Yes (20)	Died (35)
6	45/M	6	7	No	CR	No	No	negative	Alive and well (49)
7	54/M	14	6	No	CR	No	No	negative	Alive and well (61)
8	57/M	3	7	Dex	NE	NE	NE	negative	Died (7)

MP, melphalan & prednisone; Dex, dexamethasone; CR, complete remission; PR, partial remission.

* median 7 months;

** median 7 months.