
R.T. Kamble, M.D.

ORTHOTOPIC HEART TRANSPLANT FACILITATED AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN LIGHT-CHAIN AMYLOIDOSIS

Rammurti T. Kamble, M.D.

Baylor College of Medicine and The Methodist Hospital, Houston, Texas

Abstract

Initial manifestations of light-chain amyloidosis (AL) are variable and often result in missed or delayed diagnosis. Survival in AL patients depends mainly on the severity of cardiac involvement. Dominant stage-III cardiac involvement due to primary systemic amyloidosis precludes effective AL treatment and is associated with an average survival of only 3–4 months. The following paper discusses the benefits of orthotopic heart transplantation and autologous hematopoietic stem cell transplantation to improve survival in patients with progressive cardiac AL.

Introduction

Light-chain amyloidosis (AL) is a clonal plasma cell disorder characterized by clonal expansion of plasma cells that make abnormal protein. A folding defect in amyloid protein results in organ tissue deposition in the form of beta pleated sheets. Although almost every organ system may be involved, deposition in the heart, kidney, liver, intestine, and nerves accounts for most clinically relevant manifestations. Initial manifestations of AL are variable and often result in missed or delayed diagnosis. A very high index of suspicion is therefore required to establish a diagnosis of AL,[1] and the median time from initial symptoms to the diagnosis of AL is still 12 months. Survival in these patients depends primarily on the severity of cardiac involvement as reflected by elevation in serum troponin and B-type natriuretic peptide. Dominant cardiac involvement (stage III) due to primary systemic amyloidosis precludes effective AL treatment and is associated with an average survival of only 3–4 months.

Treatment of AL

Conventional treatment of AL is directed at decreasing the clone of plasma cells that produces abnormal protein. Reduction in the number of plasma cells and resultant decreased formation of abnormal protein allows dissolution of tissue amyloid, leading to organ function improvement. Clonal plasma cells can either be killed with cytotoxic chemotherapy or they can be instructed to undergo programmed cell death (apoptosis). The latter effect can now can be achieved with immunomodulatory drugs such as lenalidomide (and its analogs) or the proteosome inhibitor bortezomib. Increasing the dose of cytotoxic therapy increases the response, but dose-limiting toxicity on bone marrow cells limits the ultimate benefit that can be achieved. To circumvent the dose-limiting toxicity of cytotoxic chemotherapies such as melphalan, we collect the patient's own stem cells and store them in liquid nitrogen prior to treatment. The patient then receives otherwise lethal doses of melphalan (140–200 mg/m^2), and once the drug has been cleared from the patient, we thaw the stored stem cells and infuse them into the patient like a blood transfusion. This transplant spares the patient from the otherwise lethal effects of the drug on the marrow.[2]

Like homing pigeons, stem cells know where their home is and within hours of transplantation have settled back in the marrow. This phenomenon occurs because of receptors present on the cell surface of bone marrow stromal cells (integrin) and stem cells (selectin) that recognize corresponding structures on the stem cells and bind to them, holding the cells in place. Once these stem cells settle down in the marrow, it takes them 10–12 days to start making new blood cells. Until the new blood cells are made, patients are kept in isolation and put on prophylactic antibiotics and on blood product support as needed. Although this is a drastic treatment, transplant-related mortality is now just 1–2% from initial levels of 15% or more when the procedure was first implemented. This improvement is partly related to advances in support treatments during the period when the marrow is recovering and in larger part is attributable to better patient selection.

In the past, there have been few options available for those with dominant cardiac involvement and grade III–IV symptoms, and these patients have generally been provided with supportive and/or hospice care. Recently, however, alternative possibilities have been tried, with noteworthy responses from three patients who were thought likely to die of progressive cardiac AL within 3 months.[3, 4] These three patients initially presented with severe cardiac dysfunction as their major AL manifestation, and they underwent orthotopic heart transplantation (OHT) followed by autologous hematopoietic stem cell transplantation (ASCT). At the time their AL was diagnosed, they were 63, 62, and 44 years of age; 2 were females and 1 was male. Diagnosis of cardiac AL was established via endomyocardial biopsy, Congo red staining, and immunohistochemistry. All patients at diagnosis had end-stage heart failure and had developed cardiogenic shock that required intra-aortic balloon pump support as a bridge to OHT. They were unsuitable for ASCT or other intensive AL therapy. Following OHT, however, ASCT was performed on each patient at 13, 16, and 13 months, respectively (Table 1) before damage to the new heart could occur from their continuing AL.

All three patients were on tacrolimus and prednisone at the time of stem cell mobilization and hematopoietic transplant; two patients were also receiving mycophenolate mofetil and valganciclovir. We collected 6.1 and 6.2 x 10^6/kg CD34$^+$ cells in

Age/ Sex (months)	Time to AL diagnosis (months)	Organ involvement (months)	Time* to OHT (months)	Time to ASCT s/p OHT	Survival (months)
63/F	12	Heart, Kidney, PN	7	13	39+
62/F	24	Heart, Kidney, PN	5	16	35+
44/M	12	Heart, Kidney, tongue	4	13	23+

**Time to OHT from onset of heart failure symptoms; PN: peripheral nerve; F: female; M: male; s/p: status post.*

Table 1. Orthotopic heart transplantation (OHT) followed by ASCT.

2 days with filgrastim (5 ug/kg twice daily) and plerixafor (16 mg/kg based on day 4 $CD34^+$ counts) in two subjects. The third initially failed to mobilize, but 4.3 $x10^6$/kg $CD34^+$ cells were subsequently obtained after stopping mycophenolate mofetil for 4 weeks. The creatinine clearance at the time of high-dose chemotherapy was 36, 30, and 43 ml/min. All three patients received renal adjusted dose of melphalan at 140 mg/m^2. Mycophenolate mofetil and valganciclovir were withheld during neutropenia until engraftment. No patients received post-transplant filgrastim. Patients were hospitalized for 17, 18, and 18 days respectively. Renal function remained stable during ASCT, and nonhematological toxicity was limited to grade I–II apart from one grade-III oral mucositis and colitis. One patient achieved hematologic complete remission (patient 2) while two patients had partial response following ASCT. Remarkably, all patients are alive and well at follow-up of 23, 35, and 39 months post OHT.

Conclusion

Orthotopic heart transplantation should be considered in select patients with dominant cardiac involvement and advanced heart failure to allow subsequent ASCT and to ultimately improve survival.

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