Orthotopic Heart Transplant Facilitated Autologous Hematopoietic Stem Cell Transplantation in Light-chain Amyloidosis

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Dominant cardiac involvement by primary systemic amyloidosis (AL) precludes effective AL treatment and is associated with short survival. Between January 2009 and June 2015, total of 10 patients who presented with severe cardiac dysfunction as their major manifestation of AL underwent orthotopic heart transplantation (OHT). Five of these 10 patients were able to complete the planned second phase of treatment with autologous hematopoietic stem cell transplantation (ASCT). Diagnosis of cardiac AL was established via endomyocardial biopsy, Congo red staining and immunohistochemistry. All patients had end stage heart failure and developed cardiogenic shock requiring intra-aortic balloon pump support (median 20 days, range 10-165) as a bridge to OHT.

The median age at AL presentation was 52 years (42-63) in 5 females and 5 males. At median follow-up of 40 months (1- 65) from OHT, 7 (70 %) patients are alive (table-1). Two patients died of post-operative complications at 1 and 7 months post OHT; a 3rd patient died 36 months after OHT (23 months post ASCT) of AL progression. Five patients received ASCT at median of 13 months (13-34) after OHT. Treatment for disseminated cryptococcus delayed ASCT in one patient. In the remaining 3 patients ASCT was not feasible due; to low DLCO (n=2) and prior ASCT (n=1).

All 5 patients with ASCT 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 4.0, 5.7, 6.1 and 6.2 x 10^6/kg CD-34$^+$ cells in 2 days after filgrastim administration (5 ug/kg, twice, daily) and plerixafor (16 mg/kg based on day- 4 CD-34$^+$ counts) in 4 subjects. The fifth patient initially failed to mobilize but 4.3x10^6/kg CD-34$^+$ cells were subsequently obtained after stopping mycophenolate mofetil for 4 weeks. The creatinine clearance at the time of the high-dose chemotherapy given prior to ASCT was 36, 30, 41 43 and 53 ml/minute. All 5 patients received a renal adjusted dose of melphalan at 140mg/m^2. Mycophenolate mofetil and valganciclovir were withheld during neutropenia until engraftment. No patients received post-transplant filgrastim. Patients were hospitalized for 15, 17, 18, 18 and 20 days. Renal function remained stable during ASCT and non-hematological toxicity was limited to grade I-II apart from two grade III oral mucositis and colitis. Three patients achieved hematologic complete remission (patient2&4) while 2 patients had a partial response following ASCT. Post OHT and ASCT 4 patients are alive and well at follow-up of 38, 48, 61 and 65 months.

The strategy of OHT followed by ASCT is therefore feasible in select patients with dominant cardiac involvement and advanced heart failure

Table-1: feasibility of ASCT following orthotopic cardiac transplantation (OHT)

SN/Age/Sex	Organ involved	Time* to OHT (months)	Time§ to ASCT (months)	Factors precluding ASCT	Survival post OHT (months)	Overall survival† (months)
1 63/F	Heart, kidney, PN	7	13	NA	65+	100+
2 62/F	Heart, kidney, PN	5	16	NA	61+	94+
3 44/M	Heart, kidney, tongue	4	13	NA	38	41
4 54/F	Heart, GI, PN	1	13	NA	48+	55+
5 45/M	Heart, kidney, liver	16	NA	Prior ASCT	42+	126+
6 62/M	Heart, kidney, liver	2	NA	Death	1	11
7 54/M	Heart, liver	1	NA	Death	7	47
8 51/M	Heart, GI	1	14	NA	38+	39+
9 42/F	Heart,kidney,liver,PN	6	NA	Low DLCO	48+	55+
10 48/F	Lung, heart, GI	6	NA	Low DLCO	16+	22+

*Time to OHT from 1st OHT evaluation. §Time to ASCT from OHT, † survival from initial AL diagnosis
SN= serial number, PN= peripheral nerve, GI= gastrointestinal F= female, M= male, NA= not applicable