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Heart Transplantation, Either Alone or Combined With Liver and Kidney, a Viable Treatment Option for Selected Patients With Severe Cardiac Amyloidosis

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Background. Heart transplantation in cardiac amyloidosis (CA) patients is possible and generally considered for transplantation if other organs are not affected. In this study, we aimed to describe and assess outcome in patients following heart transplantations at our CA referral center. **Methods.** We assessed all CA patients that had heart transplantations at our center between 2005 and 2018. Patients with New York Heart Association status 3 out of 4, with poor short-term prognosis due to heart failure, despite treatment, and without multiple myeloma, systemic disease, severe neuropathic/digestive comorbidities, cancer, or worsening infections were eligible for transplantation. Hearts were transplanted by bicaval technique. Standard induction and immunosuppressive therapies were used. Survival outcome of CA patients after transplantation was compared with recipients with nonamyloid pathologies in France. **Results.** Between 2005 and 2018, 23 CA patients had heart transplants: 17 (74%) had light chain (light chain amyloidosis [AL]) and 6 (26%) had hereditary transthyretin (hereditary transthyretin amyloidosis [ATTRv]) CA. Also, 13 (57%) were male, and the mean age at diagnosis was 56.5 y (range, 47.7–62.8). Among AL patients, 13 had heart-only and 5 had heart-kidney transplantations. Among ATTRv patients, 1 had heart-only and 5 had heart-liver transplantations. The 1-y survival rate after transplantation was 78%, 70% with AL, and 100% with ATTRv. At 2 y, 74% were alive: 65% with AL and 100% with ATTRv. **Conclusion.** After heart transplantation, French CA and nonamyloid patients have similar survival outcomes. Among CA patients, ATTRv patients have better prognosis than those with AL, possibly due to the combined heart-liver transplantation. Selected CA patients should be considered for heart transplantations.

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INTRODUCTION

Heart transplantation for cardiac amyloidosis (CA) patients remains possible.[1,2] In CA patients, mechanical circulatory support, an alternative to heart transplantation, has an increased risk of death and complications compared with patients without CA[3]; however, generally, only CA patients without other organs significantly affected are considered for heart transplantation. Therefore, because donors are scarce, there is debate whether heart transplantation in CA patients is the best use of the limited hearts available. This is despite heart transplantation being a viable treatment option in severe CA patients.

Amyloidosis is a complex group of disorders characterized by the misfolding of several proteins and aggregation of amyloid fibrils in organs and tissues. Light chain amyloidosis (AL) and transthyretin (TTR) amyloidosis (ATTR) are 2 of the most frequently diagnosed.[4]

AL is the most frequent amyloidosis, and >70% have heart involvement.[4,5] AL is due to the misfolding of proteins of monoclonal plasma cells produced in bone marrow that accumulate particularly not only in the heart and kidneys but also in the gastrointestinal tract, skin, peripheral nervous system, and liver.[5,6]

ATTR is caused by misfolding of TTR predominantly produced in the liver.[5] There are 2 types of ATTR. The first, hereditary ATTR (ATTRv), is due to a hereditary mutation of a gene coding for the TTR protein, with so far >120 mutations identified.[5,7,8] The mean age of patients diagnosed with ATTRv is reported to be 62.5 y.[9] The second, wild-type ATTR (ATTRwt), results from aggregating and misfolding of wild-type TTR.[5,8] ATTRwt mainly occurs in men aged above 70 y.[5]

The patient prognosis depends on the amyloidosis type. Indeed, AL amyloidosis patients have a mortality rate up to 50% per year after the first cardiac decompensation.[5,10,11]

Furthermore, each amyloidosis type has its own arsenal of treatments. In AL-CA patients, treatment aims to remove or diminish the circulating AL amyloid fibrils (such as bortezomib-based chemotherapy) before or after heart transplantation (if appropriate), followed by autologous blood stem cell transplantation.[2,5,12] In AL-CA patients, because kidney involvement is frequent, a combined heart-kidney transplantation is often appropriate.[13] In ATTRv-CA patients, because

abnormal TTR is mainly produced in the liver, simultaneous heart-liver transplantation is an option.[14] Several studies have confirmed that heart transplantations are feasible in patients with CA, either AL or ATTR.[6,14-17]

At the Henri Mondor University Hospital in Créteil (France) at the CA referral center, heart transplantation is an option for advanced CA patients.

Our study aimed to describe and assess outcomes in CA patients after heart transplantation, either a heart-only or combined with a liver or kidney, at our institution. We here report our results together with case studies.

METHODS

We performed a retrospective study on all CA patients that underwent an orthotopic heart transplant between 2005 and 2018 at the University Hospital Henri Mondor in Creteil (France). All patients provided written informed consent before participation. This study was approved by the local institutional review board (authorization number: 1431858) and the French National Data Protection Commission (authorization number: 2215384 v 0).

Patients with suspected amyloidosis all had a complete medical evaluation when they arrived at our institution as previously described.[18,19]

Heart transplantation was indicated for patients with a New York Heart Association status 3 or 4, with a poor short-term prognosis due to heart failure, despite optimal treatment. The combined heart-kidney transplantation was proposed in cases of kidney failure with a creatinine clearance of below 35 mL/min or if the kidney biopsy detects >30% of fibrosis. The combined heart-liver transplantation was considered in cases of liver cirrhosis, proven by liver biopsy, or to reduce the amount of amyloidogenic protein. Patients with multiple myeloma, systemic disease, severe neuropathic or digestive comorbidities, cancer, or worsening infections were not eligible. Furthermore, patients with increased pulmonary vascular resistance ≥4 Wood units, after reversibility testing, were not eligible for transplantation. The final decision to perform transplantation was made by a multidisciplinary committee, including cardiologists, cardiac and liver surgeons, anesthesia and critical care medicine physicians, hematologists, nephrologists, urologists, hepatologists, neurologists, and psychologists.

In France, between 2004 and the end of 2017, organs for heart transplantations were attributed according to the urgency: starting with patients receiving intravenous inotropes that cannot be withdrawn or on short-term mechanical assistance, to patients with long-term ventricular assistance, and then to patients requiring multiorgan transplants. Since January 1, 2018, organs for transplants have been attributed according to a new allocation system based on a national score.[20] All potential organ recipients have been classified using a score comprising 4 components: the risk of death on the waiting list (according to venoarterial extracorporeal membrane oxygenation [VA-ECMO], N-terminal prohormone of brain natriuretic peptide or B-type natriuretic peptide levels, glomerular filtration rate, and total bilirubin), emergency exceptions, donor-recipient matching, and geographical location: the time required to transport the donor organ. Before 2018, patients that needed dual organ transplants had better access to organs.

Heart transplants were performed using the bicaval technique. When the heart transplant was combined with a liver or kidney transplant, the organs originated from the same donor. During the

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same surgical intervention, the heart was transplanted first, followed by the liver or kidney. Standard immunosuppressive agents for heart transplants were used combined with antithymocyte globulin or basiliximab induction, then a combination of mycophenolate mofetil, tacrolimus, and steroids for the first year after the transplant. Transplant rejection, either cellular rejection (International Society of Heart and Lung Transplantation grade ≥2R) or pathological antibody-mediated rejection, was systematically monitored by an endomyocardial biopsy 15 d after the procedure, then monthly for between 6 and 12 mo.[21] The anatomopathological evaluation of the biopsies was performed according to the International Society of Heart and Lung Transplantation guidelines.[22] During follow-up, the differences between the concentration of involved (abnormal) and uninvolved (normal) light chains (serum-free light chains) were measured in AL amyloidosis patients.

Descriptive statistics were used to describe the data. Qualitative data were reported as frequency and percentages. Quantitative data were reported as means with the associated SD. Survival was estimated using the Kaplan-Meier method, with the date of transplantation taken as reference. No formal comparisons between subgroups were planned. Consequently, *P* values reported are exploratory.

RESULTS

Baseline and Pretransplant Characteristics

Between 2005 and 2018, among 1360 patients with CA, 23 had orthotopic heart transplants at Henri Mondor (Figure 1). The patients' baseline characteristics, when registering on the cardiac transplant list, are shown in Table 1. Of the 23 patients transplanted, 17 (74%) had AL, 6 (26%) ATTRv, and none ATTRwt CA. Overall, 13 out of 23 patients (57%) were male: 8 out of 17 (47%) had AL and 5 out of 6 (83%) ATTRv. The mean age at diagnosis was 56.5 y (range, 47.7–62.8) in AL patients and 61.9 y (range, 60.1–63.7) in ATTRv patients.

Among the 6 ATTRv patients, the *TTR* gene mutations were Val122Ile in 3 patients, Ser77Phe in 1, Ser77Tyr in 1, and Glu89Lys in 1 (Table 2). Of these, 2 patients were homozygotic, both for Val122Ile. In the ATTRv patients, 5 out of 6 had combined heart-liver transplantations, and none required VA-ECMO before transplantation.

All 17 AL amyloidosis patients received at least 1 line of chemotherapy, and 7 received ≥2 lines (Table 3). The first-line chemotherapy was bortezomib and cyclophosphamide combined with dexamethasone in 11 out of 17 patients (65%). In the AL patients, 5 (29%) had a complete hematological response (CR) to treatment, 2 (12%) had a very good partial response (VGPR), 8 (47%) had a partial response (PR), 1 (6%) did not respond, and 1 (6%) received only a few days of treatment and did not have their response assessed. VA-ECMO was necessary in 3 out of 17 AL patients (18%) before transplantation: 1 for cardiovascular arrest for 20 d and 2 for refractory cardiogenic shock to dobutamine for 3 and 12 d, respectively.

Transplantation and Posttransplantation Data

The recipient, donor, transplantation, and treatment characteristics at and after transplantation are shown in Table 4. The mean age of 23 CA recipients was 60 y: 57 in 17 AL patients and 64 in ATTRv patients. All patients received induction immunosuppressive therapy: 10 with antithymocyte globulin and 13 with
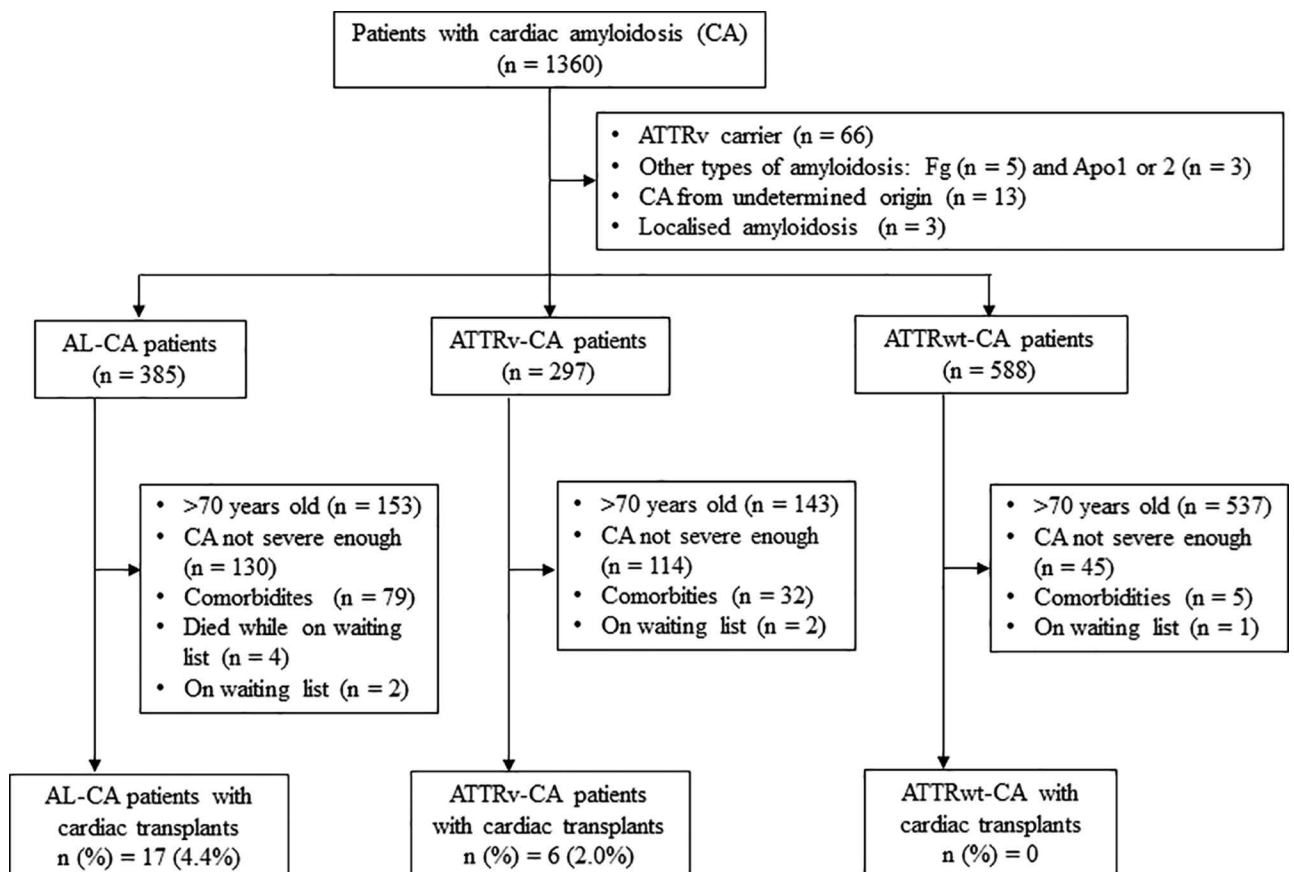

FIGURE 1. CONSORT diagram for study flow diagram. AL, light chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CA, cardiac amyloidosis.

TABLE 1.

Baseline characteristics

	All (N = 23)	AL (n = 17)	ATTRv (n = 6)	P
Amyloidosis characteristics, mean (range)				
Age at amyloidosis onset (first symptoms), y	55.6 (49.4–59.4)	56.1 (47.0–61.1)	54.9 (53.5–58.7)	0.883
Age at amyloidosis diagnosis, y	59.2 (47.7–62.8)	56.5 (47.1–61.6)	61.9 (60.1–63.7)	0.050
Kappa/lambda ratio	0.22 (0.05–1.47)	0.12 (0.04–4.54)	1.16 (0.89–1.29)	0.170
Clinical variables				
Male, n (%)	13 (57)	8 (47)	5 (83)	0.123
BMI mean (range), kg/m²	23.5 (21.6–26.0)	23.0 (21.4–25.5)	25.8 (22.9–28.5)	0.141
SBP mean (range), mm Hg	109 (100–116)	107 (98–116)	114 (102–125)	0.440
Pulse mean (range), bpm	85 (71–100)	92 (72–100)	74 (62–83)	0.150
Peripheral neuropathy, n (%)	15 (65)	9 (53)	6 (100)	**0.037**
Orthostatic hypotension, n (%)	8 (34.8)	6 (35.3)	2 (33.3)	0.931
Cardiac pacemaker implant, n (%)	4 (17)	3 (18)	1 (17)	0.957
Biological variables, mean (range)				
NT-proBNP, pg/mL	5842 (4608–9555)	7825 (5414–12 072)	3057 (2352–5440)	**0.003**
cTnT HS, ng/mL	90 (63–129)	110 (74–174)	64 (39–66)	**0.016**
Creatinine, µmol/L	93 (82–113)	93 (77–115)	94 (84–111)	0.912
Hemoglobin, g/dL	13.2 (11.9–14.6)	13.2 (11.5–14.7)	13.3 (11.9–13.9)	1.000
ASAT, IU/L	34 (28–40)	31 (27–39)	38 (33–57)	0.150
ALAT, IU/L	30 (23–48)	29 (21–46)	34 (24–54)	0.396
Total bilirubin, µmol/L	13.0 (8.5–18.0)	11.5 (7.5–17.0)	16.5 (12.0–46.5)	0.112
GGT, IU/L	117 (56–243)	82 (55–157)	253 (109–377)	0.090
Alkaline phosphatase, IU/L	93 (74–140)	88 (75–134)	122 (73–187)	0.417
Albumin, g/L	36.4 (29.2–40.5)	33.4 (28.4–40.2)	38.2 (36.2–41.3)	0.132
Gamma-globulin, g/L	8.4 (4.3–11.2)	6.6 (3.8–9.2)	10.6 (8.3–17.5)	0.050
Echocardiographic variables, mean (range)				
IVST, mm	18 (16–21)	17 (15–19)	22 (20–26)	**0.007**
LVEF, %	47 (41–57)	48 (45–62)	36 (24–51)	0.063
GLS, %	7.4 (5.9–8.5)	7.3 (5.5–8.8)	7.5 (6.1–8.4)	0.846
TAPSE, mm	13.5 (10.0–18.25)	12.5 (10.0–16.0)	15.5 (13.5–19.5)	0.199
S' wave, cm/s	9.0 (8.0–11.0)	9.0 (8.0–11.3)	9.5 (9.0–11.0)	0.530
RA dilatation, n (%)	18 (90)	13 (93)	5 (83)	0.515
IVC dilatation, n (%)	16 (76)	11 (73)	5 (83)	0.627
RAP, mm Hg	13 (8–16)	13 (7–17)	13 (10–17)	0.965
RA/PCWP	0.58 (0.43–0.81)	0.58 (0.37–0.84)	0.60 (0.49–0.82)	0.725
Right heart catheterism, mean (range)				
sPAP, mm Hg	39.5 (32.5–51.3)	38.5 (30.3–51.0)	48.0 (34.5–60.5)	0.196
mPAP, mm Hg	29.0 (24.0–36.3)	29.0 (24.0–36.8)	30.0 (22.3–39.0)	1.000
PCWP, mm Hg	19.0 (17.8–26.0)	19.0 (18.0–23.8)	21.0 (13.3–31.3)	0.824
Cardiac index, L/min/m²	2.3 (2.0–2.6)	2.3 (2.0–2.6)	2.4 (2.0–2.9)	0.868
PVR, Wood units	2.0 (1.1–3.0)	2.3 (1.1–3.1)	2.0 (1.3–2.5)	0.568

Bold value was for highlight $P < 0.05$.
AL, light chain amyloidosis; ALAT, alanine transaminase; ASAT, aspartate transaminase; ATTRv, hereditary transthyretin amyloidosis; BMI, body mass index; bpm, beats per minute; cTnT HS, high-sensitivity troponin T; GGT, gamma-glutamyl transferase; GLS, global longitudinal strain; IVC, inferior vena cava; IVST, interventricular septal thickness; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

TABLE 2.

Transthyretin amyloidosis–specific treatment and type of organ transplant in the hereditary transthyretin amyloidosis patients

Patient no.	Sex	Age[a]	*TTR* mutation	Year[b]	Organ(s) transplanted	Details during follow-up
1	M	57	Val122Ile (p.Val142Ile) homozygous	2018	Heart and liver	Neurologically stable. Alive.
2	M	59	Val122Ile (p.Val142Ile) heterozygous	2018	Heart and liver	Neurologically stable. Alive
3	M	63	Ser77Phe (p.Ser97Phe) heterozygous	2016	Heart and liver	Neurologically stable. Alive
4	M	65	Ser77Tyr (p.Ser97Tyr) heterozygous	2016	Heart	Since 2015, treated with tafamidis. Since 2019, aggravation of peripheral neuropathy. In 2020, initiated patisiran. Alive
5	F	66	Glu89Lys (p.Glu109Lys) heterozygous	2015	Heart and liver	Despite, tafamidis treatment aggravation of neuropathy, dysautonomia, and digestive symptoms. In 2020, initiated patisiran. Alive.
6[c]	M	62	Val122Ile (p.Val142Ile) homozygous	2012	Heart and liver	Neurologically stable. Alive

[a]Age at transplantation.
[b]Year of transplantation.
[c]Patient's liver was used for a domino transplant.
F, female; M, male.

TABLE 3.

Details concerning light chain amyloidosis patients

Patient no.	Sex	Age[a]	Mayo Clinic status	First-line chemotherapy (second, then third lines)	Hematological response[b]	Year[c]	Organ(s) transplanted	Amyloidosis relapse	Status (December 2020)
7	Female	53	IIIa	B, C, and D (B, C, D, and dara, then B, D, and dara)	VGPR	2018	Heart	No	Alive
8	Male	47	IIIb	B, C, and D (dara, then V and C)	NA[d]	2018	Heart and kidney	No	Alive
9	Male	63	IIIa	B, C, and D	PR	2018	Heart	No	Deceased <30 d (dysfunction of the transplanted organ in 2018)
10	Female	65	IIIa	B, C, and D	CR	2018	Heart	No	Alive
11	Female	56	IIIa	B, C, and D	CR	2018	Heart	No	Alive
12	Female	61	IIIb	B, C, and D	CR	2018	Heart and kidney	No	Alive
13	Male	63	IIIa	B, C, and D (B and D)	PR	2017	Heart and kidney	No	Deceased at 3 mo (septic shock-pulmonary in 2017)
14	Female	59	IIIa	B, C, and D	CR	2017	Heart	Yes (kidney)	Alive
15	Male	48	IIIa	B, C, and D	PR	2017	Heart	Yes (heart and kidney)	Alive
16	Male	43	IIIb	B, C, and D	No response	2017	Heart	No	Deceased at 3 mo (pneumonia in 2017)
17	Male	62	IIIb	B, C, and D (B, R, and D)	PR	2016	Heart and kidney	Yes (multiple myeloma with bone lesions)	Deceased at 20 mo (septic shock in 2018)
18	Male	48	IIIb	B, M, P	PR	2016	Heart		Deceased at 5 mo (septic shock in 2016)
19	Female	48	IIIb	B, C, and MTX	PR	2016	Heart		Deceased at 3 mo (femoral artery rupture in 2016 following ECMO support)
20	Female	57	IIIb	M and prednisone (B, C, and D, then dara)	PR	2014	Heart	Yes (kidney)	Deceased at 4 y (sepsis in 2018)
21	Female	47	IIIb	B, D, and M (B, C, and D, then V, R, and D)	VGPR	2013	Heart	Yes (kidney)	Alive
22	Female	58	IIIa	B, D, and M	CR	2012	Heart	No	Alive
23	Male	47	UK	V, A, and P (M and D)	PR	2005	Heart and kidney	Yes (kidney)	Deceased at 11 y (sudden death in 2016)

Bold value was for highlight *P* < 0.05.

[a]Age at transplantation.

[b]Hematological response before transplantation.

[c]Year of transplantation.

[d]Patient had treatment a few days before the transplantation and thus did not have time to evaluate a response.

A, adriamycin; B, bortezomib; C, cyclophosphamide; CR, complete hematological response; D, dexamethasone; dara, daratumumab; ECMO, extracorporeal membrane oxygenation; M; melphalan; MTX, methotrexate; NA, not available; P, prednisone; PR, partial response; R, lenalidomide; TTR, transthyretin; UK, unknown; V, vincristine; VGPR, very good partial response.

basiliximab. Overall, 13 patients had heart-only, 5 (all ATTRv) had heart-liver, and 5 (all AL) had heart-kidney transplants.

Among the 6 ATTRv amyloidosis patients, the first and second patients transplanted had combined heart-liver transplants for metabolic reasons. The third patient had a heart-only transplant because an ATTR-specific treatment became available. The subsequent 3 patients were proposed heart-liver transplant due to extensive fibrosis or cirrhosis on liver biopsy. Of the 5 AL amyloidosis patients who had combined heart-kidney transplantations, 1 was dialyzed when registering for transplantation, 3 had creatinine clearance below 35 mL/min, and 1 patient had a creatinine clearance of 45 mL/min but with 50% interstitial fibrosis on kidney biopsy. Emergency transplantations were performed in 9 (39%) patients: 7 out of 17 (41%) with AL and 2 out of 6 (33%) with ATTR. VA-ECMO was necessary in 6 out of 23 patients (26%) after transplantation due to primary graft dysfunctions, all with AL amyloidosis, and including 3 that had VA-ECMO implanted before transplantation. At transplantation, the median serum-free light chains level in AL patients was 39 mg/L (interquartile range, 14.9–84.0). Interestingly, in AL patients without complete hematological responses before transplantations, the light chain levels diminish during the immunosuppressive therapy.

Posttransplantation Survival in Heart-Transplanted CA Patients

At 1 y after transplantation, 18 out of 23 patients (78%) were alive: 12 out of 17 (70%) of AL patients and 6 out of 6 (100%) of ATTR (Figures 2 and 3). Similarly, at 2 y after transplantation, 17 out of 23 patients (74%) were alive: 11 out of 17 (65%) with AL and 6 out of 6 (100%) with ATTRv. One patient died within 1 mo of the transplantation from pulmonary septic shock. At analysis, 8 out of 23 patients have died, all AL patients (Table 3). Death was due to sepsis in 5 patients. The remaining 3 deaths were due to dysfunction of the heart, femoral triangle rupture at the VA-ECMO site due to systemic candidiasis, and sudden death. Three of the patients who died of infection had amyloidosis relapse in the kidney. The case studies for patients 18 and 23 are described in the Supplemental Digital Content (**SDC,** http://links.lww.com/TXD/A420).

TABLE 4.

Characteristics of the recipient, type of transplant, and follow-up data in the overall cohort and depending on the type of amyloidosis

	All (N = 23)	AL (n = 17)	ATTRv (n = 6)	*P*
Recipient characteristic at heart transplantation				
Age at heart transplant, mean (range), y	60 (48–64)	57 (48–62)	64 (61–65)	0.036[a]
ABO blood group, n (%)				0.913
A	6 (26)	4 (24)	2 (33)	
AB	1 (4)	1 (6)	0 (0)	
B	4 (17)	3 (18)	1 (17)	
O	12 (53)	9 (52)	3 (50)	
Organ transplanted combined with the heart				<0.001[a]
Liver, n (%)	5 (22)	0 (0)	5 (83.3)	
Kidney, n (%)	5 (22)	5 (30)	0 (0)	
Creatinine, mean (range), μmol/L	114 (88–168)	117 (83–172)	114 (104–169)	0.854
Bilirubin, mean (range), μmol/L	14.0 (6.9–18.0)	8.5 (6.0–17.0)	17.5 (14.0–27.3)	0.049[a]
NT-proBNP, mean (range), pg/mL	6070 (4401–10 242)	7957 (4925–21 389)	4581 (3645–5759)	0.062
GFR, mean (range), mL/min	55 (39–72)	52 (37–70)	63 (42–75)	0.417
dFLC, mean (range), mg/L		39 (10–112)		
Ascites, n (%)	2 (9)	1 (6)	1 (17)	0.449
Cardiac management at the time of transplantation, n (%)				
Inotrope pre-HT	5 (22)	4 (24)	1 (17)	0.726
VA-ECMO pre-HT	3 (13)	3 (18)	0 (0)	0.270
Emergency heart transplant	9 (39)	7 (41)	2 (33)	0.735
Organ donor characteristics				
Age, range, y	53 (36–62)	52 (36–62)	57 (42–68)	0.344
Male, n (%)	11 (48)	5 (29)	6 (100)	0.003[a]
Transplantation and 1 mo postmanagement, n (%)				
Donor organ ischemic duration, mean (range), min	155 (122–220)	182 (119–232)	138 (125–208)	0.441
VA-ECMO post-HT	6 (26)	6 (35.3)	0 (0)	0.091
ALG	10 (43)	7 (41)	3 (50)	0.708
Basiliximab	13 (57)	10 (59)	3 (50)	
Dialysis post-HT	7 (30)	5 (29)	2 (33)	0.858
Graft rejection[b]	4 (17)	4 (24)	0 (0)	0.191
Survival at 1 mo, n (%)	22 (96)	16 (94)	6 (100)	0.544
Follow-up post transplantation, mean (range), d	468 (157–1471)	439 (134–1160)	906 (308–1749)	0.263

[a]*P* is significant.
[b]ISHLT grade ≥2R or pAMR2.
AL, light chain amyloidosis; ALG, antilymphocyte globulin; ATTRv, hereditary transthyretin amyloidosis; dFLC, serum-free light chains; GFR, glomerular filtration rate; HT, heart transplantation; ISHLT, International Society of Heart and Lung Transplantation; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; pAMR2, pathological antibody-mediated rejection; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

DISCUSSION

The survival outcomes after heart transplantation in the 23 patients in our series are comparable with recipients with nonamyloid pathologies in France. Indeed, in France, the 1-y
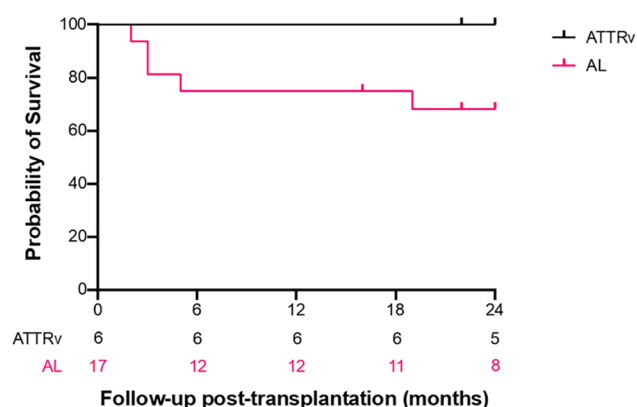
FIGURE 2. Kaplan-Meier curve of survival in cardiac amyloidosis patients after heart transplantation. AL, light chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis.

survival rate for heart-transplanted patients has continued to increase from 72.3% reported between 2005 and 2008 to 80.6% between 2017 and June 2018.[23] We observed a 1-y overall survival rate of 78%: 100% in ATTRv and 70% in AL amyloidosis patients.

In AL amyloidosis patients, outcomes were better in patients with CR or VGPR; indeed, all of these patients were alive at analysis. Patients with PR or no hematological response had worse outcomes: 1 died of amyloidosis relapse 20 mo after transplantation, 1 had a graft dysfunction, and the remaining patients had sepsis.

Interestingly, survival was prolonged in ATTRv compared with AL patients. At analysis, after a follow-up of ≥3 y, all ATTRv amyloidosis patients are still alive. A recent single-center study compared outcomes in 18 AL and 21 ATTR amyloidosis patients (16 ATTRv and 5 ATTRwt).[24] The study also reported that survival rates after heart transplantation were higher in ATTR amyloidosis patients. Interestingly, a German study assessed outcomes of patients with heart-transplanted during 2 time periods: 2002 to 2007 and 2008 to 2017.[6] The study concluded that survival outcomes for AL-CA patients were better and were comparable with nonamyloidosis patients in the modern era (2008 to 2017). Moreover, a
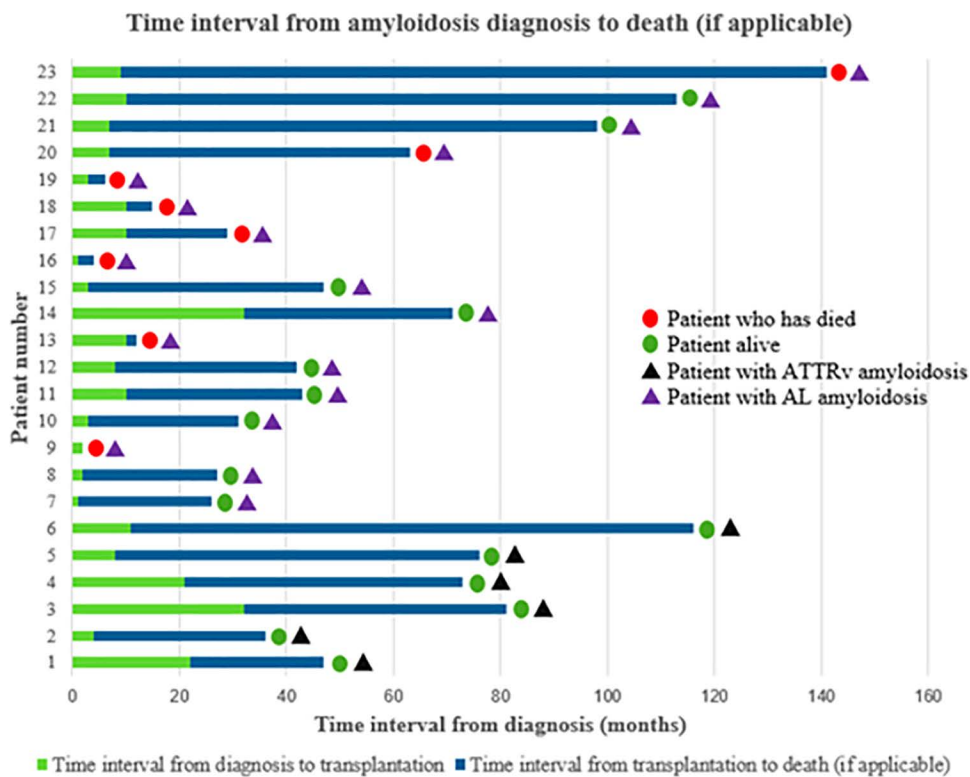
FIGURE 3. Swimmer plot of survival in cardiac amyloidosis patients from diagnosis to transplantation and through follow-up. AL, light chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis.

single-center study reviewed the data of 19 patients with amyloidosis that underwent heart transplantation between August 2008 and October 2013.[15] Of the 19 patients, 9 had AL, and 10 had ATTR amyloidosis. Survival outcomes were better in AL amyloidosis patients than those with ATTR amyloidosis. Furthermore, survival outcomes in patients, after heart transplantation, with CA were better than those of patients without CA at the institution. A recent study evaluated 31 patients, 13 with AL and 18 with ATTR amyloidosis, that underwent heart transplants at a single center between 2004 and 2017[16]; however, survival was similar in AL and ATTR amyloidosis patients. Furthermore, survival was not significantly different in the 19 patients with CA compared with the 599 without CA that underwent heart transplantation during the same period.

In CA patients, particularly in ATTRv-CA patients, multiorgan transplantations are often required. In our study, 5 out of 6 ATTRv patients had heart-liver transplants. In the single-center study reported by Griffin et al,[24] of the 21 ATTR patients, 7 had heart-liver transplants. Our results show that multiple organ transplantations are feasible in CA patients and appear to have better outcomes than heart-only transplants.

In our series of 6 ATTRv patients, 2 males were homozygote for Val122Ile. Considering the rarity of homozygote Val122Ile,[25] this may suggest that homozygous and heterozygous ATTRv patients may have different disease evolution. Indeed, homozygous compared with heterozygous patients tend to be younger when they show severe cardiac involvement.[26]

Interestingly, our results suggest that evolution of neuropathy and stability of the liver transplanted may depend on the *TTR* gene mutation. Indeed, the 3 patients with Val122Ile have a better prognosis than ATTRv patients with other mutations. Also, the only patient without a liver transplantation

developed a severe neuropathy not stabilized despite current ATTR treatments. Indeed, heart transplantation changed the natural history of the disease. Indeed, our patients without cardiac transplantation would have died of heart failure; however, transplantation allowed amyloid infiltration to infiltrate other organs, particularly nerves. The good outcomes of ATTRv patients with heart-liver transplantations suggest that combined transplants should be used when possible. Also, the probable amyloid evolution must be assessed when considering transplantation. Furthermore, liver transplants in ATTRv patients seem to protect the heart from rejection and give better prognosis. Alternatively, the liver graft may increase the tolerance of other allografts.[27,28] Indeed, it has been reported that simultaneous liver transplants lower the risk of cardiac allograph rejection.[28]

In our cohort, among the 5 patients with heart-liver transplantations, 2 patients had preexisting donor-specific HLA antibodies at transplantation, and the remaining 3 developed de novo donor-specific antibodies, including 1 with a cardiac allograft rejection, 7 mo after being transplanted. The mean fluorescence intensity values then decreased. Compared with patients with heart-only transplantations or heart-kidney transplantations, patients with heart-liver transplantations had less rejection with 1 out of 6 (17%), compared with 6 out of 18 (30%).

In our study, most patients (74%) had AL amyloidosis. The Mayo Clinic has reported outcomes from a retrospective analysis of 23 AL amyloidosis patients undergoing heart transplantation: 52% were female, and the average age at transplantation was 53 y.[29] Most of these patients, 21 out of 23 (91%), had heart-only involvement. The other patients had peripheral neuropathies, 1 with gastrointestinal involvement. In contrast, 53% of our AL amyloidosis patients had peripheral neuropathy with cardiac involvement. Furthermore, in

the Mayo Clinic series, 96% of patients had heart-only transplants. Only 1 patient had a kidney-heart transplantation. Another 2 patients had kidney transplantations at 23 and 53 mo after the heart transplantations. In comparison, 30% of our AL patients had kidney-heart transplantations.

In our study, all but 1 of the AL patients received chemotherapy before transplantation. Our patients responded well to chemotherapy. Indeed, of the 16 patients treated before transplantation, 29% had a CR, 12% a VGPR, and 47% a PR. Only 1 patient did not respond to treatment. Interestingly, in the Mayo Clinic series, only 17% of patients had chemotherapy before transplantation; 83% were administered posttransplantation chemotherapy.[29] AL amyloidosis patients who received pretransplantation chemotherapy have a risk of fatal pulmonary infections during the first year after transplantation. One of our patients died of pulmonary septic shock about 3 mo after transplantation. Consequently, precautions that could lower the risk of death during the first year after transplantation should be considered, including stopping chemotherapy before transplantation, even without complete hematological response, to improve patient health status before transplantation. Furthermore, immunoglobulin supplements could be proposed in patients with hypoglobulinemia. Interestingly, Kastritis et al[30] recently reported that adding daratumumab to first-line treatment for AL amyloidosis increased the hematological complete response rates and survival without major organ deterioration or hematological progression rates. Thus, daratumumab combined with bortezomib, cyclophosphamide, and dexamethasone is becoming the standard for treating AL amyloidosis. The role of transplantation with this and other therapeutic advances will need to be accessed.

In the Mayo Clinic series, the overall survival rate after transplantation was 77% at 1 y and 65% at 2 y.[29] Also, a 1-y overall survival rate of 75% was reported in a series of 8 French AL patients.[31] In the AL amyloidosis patients in our study, we observed a 70% survival rate at 1 y and 65% at 2 y.

Interestingly, 7 patients in the Mayo Clinic series had a complete hematological response to AL treatment. The median survival in these patients was >10 y compared with 3.5 y in the overall series. Today in France, numerous AL patients die waiting for heart transplantation. Waiting for a complete response before transplantation may not be optimal considering the risk of death in these patients. Indeed, there are currently several approved therapies that effectively reduce light chains.

The 2 case studies that we present (Supplemental Digital Content, SDC, http://links.lww.com/TXD/A420) show that immunosuppressive treatment lowers the light chain levels. In the case of patient 23, a complete hematological remission was observed without requiring the autonomous stem cell transplant initially planned. The other patients benefited from new therapies in hematology, such as bortezomib and daratumumab.[32-36]

Consequently, considering the survival benefits, heart transplantation should be proposed in selective AL amyloidosis patients even before a complete hematological response has been achieved.

Overall, 39% of our patients (41% with AL and 33% with ATTRv) had emergency heart transplantation. Interestingly, a single-center study in Spain compared elective and emergency heart transplants and found that emergency transplants were more costly with lower survival rates.[37] The authors

suggest that donor scarcity has prolonged waiting time to transplantation but also the number of emergency transplantation. Approximately, 50% of Spanish heart transplantation patients have emergency transplantation compared with the 39% in our study.

Today, the use of induction therapy, as part of immunosuppressive therapy, before heart transplantation remains controversial. The aim of induction therapy is to suppress the immunity during the early postoperative stage preventing early transplant rejection.[38] Furthermore, induction therapy delays nephrotoxic immunosuppression initiation with calcineurin inhibitors and facilitates the stopping of glucocorticoids after transplantation; however, although induction therapy effectively decreases early transplant rejection, it is associated with increased rates of infections.[38] There is also no evidence that induction therapy has survival benefits.[39] In 2018, a systematic review and meta-analysis reported that about 50% of heart transplantation patients received induction therapy: 30% received interleukin-2 receptor antagonists and the remaining 20% polyclonal antithymocyte antibodies.[38] In our study, all patients received induction therapy with antithymocyte globulin or basiliximab. Overall, 5 patients died within 1 y of transplantation. Among these, death was due to septic shock in 3 patients: 1 during the first month posttransplantation, 1 after 3 mo, and 1 after 5 mo. Of the patients who died of septic shock, 2 had basiliximab and 1 thymocyte globulin induction therapy.

The remaining 3 AL patients died >1 y after transplantation; the causes of death were sepsis shocks. We, here, provide evidence that heart transplantation either alone or combined with a liver or kidney transplant is feasible for CA patients and provides comparable outcomes to nonamyloidosis patients following heart transplantation; however, careful patient selection remains critical to optimize the use of available organs but also outcomes. However, today, amyloidosis patients should be considered for heart transplants.

Our study has several limitations. Despite our study being one of the largest conducted in heart-transplanted CA patients, the limited number of patients makes it difficult to draw definitive conclusions. Furthermore, we have not discussed or analyzed donor characteristics that are varied and impact outcomes.

CONCLUSIONS

Heart transplantation in CA patients results in survival benefits similar to those observed in nonamyloid transplant patients. Prognosis is better in ATTRv patients than AL patients, and the good prognosis of ATTRv might be due to the combined heart-liver transplantation. In AL patients, outcomes are better in those with complete hematological remission, although some with partial remission were still alive at analysis. Our results also suggest that waiting for a complete hematological response before transplantation in AL patients may not be optimal in terms of survival. Consequently, carefully selected CA patients should be considered for heart transplantations.

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