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Heart transplantation in systemic (AL) amyloidosis: A retrospective study of eight French patients

Transplantation cardiaque et amylose AL en France : étude rétrospective de huit observations

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Summary

Background. — Immunoglobulinic (AL) amyloidosis is a complication of plasma cell dyscrasia, characterized by widespread deposition of amyloid fibrils derived from monoclonal light chains. Cardiac amyloid is the main prognostic factor, with a median survival of six months. Cardiac transplantation in AL amyloidosis is associated with high mortality, due to disease recurrence in the allograft and systemic progression. Suppression of light chain (LC) production

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chains;
Heart transplantation;
NT-pro-BNP

with chemotherapy by melphalan plus dexamethasone (MD) or high dose melphalan followed by autologous stem cell transplantation (HDM/ASCT) improves survival. However, both the indications and results of chemotherapy in patients transplanted for cardiac AL amyloidosis remain unclear.

Aims. — To assess the outcome of cardiac transplantation and haematological therapy in patients with cardiac AL amyloidosis.

Methods. — Eight French patients, who underwent heart transplantation for cardiac AL amyloidosis between 2001 and 2006 were studied retrospectively.

Results. — Before transplantation, six patients received MD ($n = 5$) or HDM/ASCT ($n = 1$). Haematological remission was obtained in three patients treated with MD. In the three remaining patients, postoperative HDM/ASCT ($n = 2$) or allogeneic bone marrow transplantation ($n = 1$) resulted in haematological remission in one patient. In 2 patients not treated before transplantation, post-operative treatment with MD resulted in complete hematological remission in one. After a median follow-up of 26 months from cardiac transplantation, six patients were alive and four had sustained haematological remission, as indicated by normal serum free LC levels.

Conclusion. — Appropriate haematological therapy, including MD, may result in a survival benefit in AL amyloidosis patients with advanced heart failure requiring transplantation.

MOTS CLÉS
Amylose AL ;
Cardiopathie restrictive ;
Chaînes légères libres sériques ;
Transplantation cardiaque ;
NT-proBNP

Résumé

Avant propos. — L'atteinte cardiaque conditionne le pronostic de l'amylose AL, avec une médiane de survie inférieure à six mois. La transplantation cardiaque (TxC) dans l'amylose AL est associée à une mortalité élevée, liée à la récidive sur le greffon des dépôts de chaînes légères (CL) d'immunoglobuline monoclonale et à la progression systémique de la maladie. La suppression de la production de CL par la chimiothérapie conventionnelle par melphalan et dexamethasone (MD) ou le traitement intensif par melphalan haute dose et autogreffe de cellules souches hématopoïétiques, permet d'améliorer la survie. Cependant, les indications et les résultats de la chimiothérapie chez les patients transplantés cardiaques pour une amylose AL demeurent mal connus.

Objectifs. — Évaluer les résultats de la transplantation cardiaque (TxC) dans l'amylose AL en France.

Méthodes. — Huit patients greffés cardiaques entre 2001 et 2006 pour une cardiopathie amyloïde AL ont été étudiés rétrospectivement.

Résultats. — Avant la TxC, cinq patients ont reçu une chimiothérapie par MD et un patient un traitement intensif, avec une rémission hématologique dans trois cas. Chez les trois patients non-répondeurs, le traitement intensif post-TxC avec autogreffe ou allogreffe de moëlle (un patient) a entraîné la rémission hématologique dans un seul cas. Sur deux patients non traités avant la greffe cardiaque, une rémission hématologique complète a été obtenue dans un cas après une chimiothérapie par MD en postopératoire. Avec suivi de 26 mois postgreffe, six patients sont vivants et quatre en rémission hématologique prolongée.

Conclusion. — Un traitement hématologique approprié, notamment la chimiothérapie de type MD permet une survie prolongée chez les patients greffés cardiaques pour une cardiopathie amyloïde AL.

Abbreviations

ABMT allogeneic bone marrow transplantation
AL immunoglobulinic
BNP brain natriuretic peptide
HDM/ASCT high dose melphalan + autologous stem cell transplantation
LVEF left ventricular ejection fraction
MD melphalan plus dexamethasone
NT-proBNP N-terminal pro-brain natriuretic peptide
NYHA New York Heart Association
sFLC serum free light chain

Background

AL amyloidosis is a systemic disorder, usually caused by a smouldering clonal plasma cell disorder producing monoclonal light chains (LC) that undergo conformational modifications and aggregate into amyloid fibrils [1]. Amyloid fibril deposits commonly affect the kidneys, heart, liver, and peripheral and autonomic nervous system [2]. Restrictive cardiomyopathy is a severe and frequent complication of AL amyloidosis, with a 20% prevalence of symptomatic cardiomyopathy at diagnosis. Clinical manifestations progress over time, ranging from asymptomatic electrocardiographic

changes (low voltages in the limb leads) to rhythm abnormalities, atheroembolism, myocardial ischaemia, conduction blocks, heart failure, and sudden death. The overall prognosis of patients with AL amyloidosis is poor, ranging from 12 to 24 months. Cardiac amyloid is the main prognostic factor, with a median survival of approximately nine months in symptomatic patients and less than six months at the stage of congestive heart failure [3].

Cardiac transplantation has been performed in a small number of patients with AL amyloidosis [4—13]. Its indication remains controversial because of organ shortage, recurrence of amyloid deposition in the graft, and progression of the disease, with severe systemic symptoms related to widespread organ involvement. Recent reports have shown encouraging results, with long-term survival in patients with AL amyloidosis and predominant cardiomyopathy after sequential heart transplantation followed by high dose melphalan therapy and autologous stem cell transplantation (HDM/ASCT) [10] or even allogeneic bone marrow transplantation (ABMT) [11]. In heart recipients, in whom remission of the underlying plasma cell disorder is achieved with HDM/ASCT, amyloid deposits do not recur in the allograft and the systemic progression of the disease is stopped, resulting in prolonged survival [10]. However, this procedure is applicable only to selected cases, as many patients with multiple organ deposits are not eligible for HDM/ASCT because of high treatment-related mortality [14]. We report here the French experience of heart transplantation for amyloid heart disease from 2001 to 2006. At variance with other previous reports, all patients had multiple organ involvement at the time of transplantation.

Methods

All patients who underwent cardiac transplantation for AL amyloid cardiomyopathy were identified by questioning the databases of the 13 French heart transplant centres. The diagnosis of AL amyloidosis was confirmed histologically in all cases by immunofluorescence or immunohistochemistry performed on cardiac or extracardiac biopsy samples, using specific antilambda or antikappa conjugates. Demonstrations of underlying plasma cell dyscrasia was searched for in all patients using bone marrow smears and/or trephine, coupled with serum and urine immunoelectrophoresis. Serum free light chain (sFLC) levels were measured, whenever possible, with the Freelite® nephelometric assay (Binding Site,

Birmingham, UK), which became available for use in 2003. The normal ranges of kappa and lambda light chains are 3.6—16 mg/L and 8.10—33 mg/L, respectively, and the normal range for the kappa/lambda ratio is 0.36—1 mg/L. Organ involvement was defined according to the Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis [15]. The diagnosis of amyloid heart disease was assessed as follows: presence of low voltage on 12-lead electrocardiography, associated with features of hypertrophic cardiomyopathy (mean septum thickness greater or equal to 12 mm in the absence of other potential causes of left ventricular hypertrophy) [15]. Systolic function was evaluated using Simpson's method of estimation of left ventricular ejection fraction (LVEF). When available, serum N terminal pro brain natriureticpeptide (NT-proBNP) levels were monitored using an electrochemiluminescence immunoassay (Roche, Basel, Switzerland). Complete haematological response to treatment was defined as the complete disappearance of the monoclonal immunoglobulin or light chain in a serum or urine specimen; partial haematological response was defined as greater than 50% reduction in these proteins. Baseline clinical characteristics, survival outcomes and mortality for the entire cohort were also analysed. Two cases from the present series were reported previously [12,13].

Results

From 2001 to 2006, eight patients (five men, three women) aged 48.5 ± 10.7 years (range 29—62) at the time of AL amyloidosis diagnosis, underwent cardiac transplantation in France. Main baseline clinical and haematological characteristics are shown in Tables 1 and 2. Histological diagnosis of AL amyloidosis was established on skin ($n = 4$), endomyocardial ($n = 3$) and kidney ($n = 1$) biopsies, with amyloid deposits composed of lambda light chains in six cases and kappa light cases in two patients. A serum and/or urine monoclonal component was found in all cases. Only two patients had significant plasma cell bone marrow infiltration, indicative of smouldering myeloma.

All patients had severe systemic involvement at presentation, with a mean number of 4.3 (range 3—7) affected organs or tissues at presentation. Extracardiac amyloid accumulation was detected in the skin/soft tissue ($n = 7$), kidney ($n = 6$), peripheral nervous system ($n = 6$), liver ($n = 4$), upper digestive tract ($n = 3$), and lung ($n = 1$). Five of

Table 1	Patient baseline characteristics.				
Patient	Sex	Age (years)	Light chain	% PC	Histology
1	Male	29	Lambda	< 10	Endomyocardial biopsy
2	Male	60	Kappa	< 10	Skin biopsy
3	Female	56	Lambda	5	Skin biopsy
4	Male	62	Lambda	29	Skin biopsy
5	Female	47	Lambda	8.5	Endomyocardial biopsy
6	Female	43	Kappa	2	Endomyocardial biopsy
7	Male	46	Lambda	< 10	Skin biopsy
8	Male	45	Lambda	10	Kidney biopsy
% PC, percentage of mature plasma cells on bone marrow biopsy/smears.					

Table 2 Clinical, electrocardiographic, biological and echocardiographic data before heart transplantation.

Patient	NYHA classification	Edema	AVB	LV	PRW	BNP* (pmol/L; N < 200) or NT-proBNP (pmol/L; N < 300)	SCr (μmol/L)/Uprot (g/24 hours)	SW/PW (mm)	RP	LAD	PE	LVEF (%)
1	3	Yes	Yes	No	No	ND	77/3.1	18/20	Yes	Yes	Yes	25
2	3	Yes	Yes	Yes	No	1,100*	91/1.4	15/17	Yes	Yes	Yes	55
3	3	Yes	Yes	Yes	No	ND	58/0.3	12/12	Yes	Yes	No	60
4	3	Yes	No	Yes	Yes	4,000*	62/0.7	19/18	Yes	Yes	Yes	37
5	3	Yes	No	No	Yes	ND	128/1.1	15/15	Yes	ND	Yes	35
6	3	Yes	No	Yes	Yes	ND	95/0.5	15/12	Yes	ND	No	40
7	2	Yes	No	No	No	ND	83/16	ND	Yes	ND	Yes	60
8	3	Yes	Yes	Yes	Yes	10,870	90/2.1	17/13	Yes	Yes	Yes	23

AVB: first-degree atrioventricular block; LAD: left atrial dilatation; LV: low voltage; ND: no data; PE: pericardial effusion; PRW: poor R-wave progression in precordial leads; PW: posterior wall thickness; RP: restrictive pattern on transmitral Doppler flow; SCr: serum creatinine; SW: septum wall thickness; Uprot: proteinuria.

the six patients with renal involvement presented initially with nephrotic syndrome (Tables 1 and 3).

Cardiac manifestations were prominent at presentation: all patients had severe fluid retention, with NYHA class 3 heart failure in seven cases. Electrocardiography showed diffuse low voltage in five patients and first degree atrioventricular conduction block associated with poor R wave progression in the precordial leads in four patients (Table 2). In the three patients for whom BNP/NT-proBNP tests were available, high serum levels were found at the time of diagnosis (Table 2). Echocardiography findings were reviewed in seven cases. Restrictive cardiomyopathy was present in all patients, associated invariably with left ventricular and septal thickening (Fig. 1). Left atrial dilatation and pericardial effusion were observed in 6/6 and 6/8 patients, respectively. Five patients had evidence of advanced amyloid heart failure, with a left ventricular ejection fraction (LVEF) less than 50%.

Prior to heart transplantation, five patients received chemotherapy with oral melphalan plus dexamethasone (MD) (Table 3); only patient six was offered intensive therapy with HDM/ASCT. Serial monthly measurements of sFLC levels were performed in only two patients before and after MD therapy. Partial haematological response was obtained after three courses of MD in patient 2. In patient 8, complete haematological response was observed after three courses of MD, as illustrated by a rapid 80% reduction in the aberrant sFLC concentration, with a parallel decrease in NT-proBNP levels (Fig. 3).

The mean time between the diagnosis of amyloid cardiomyopathy and heart transplantation was 8.1 ± 7.9 months (Table 4). The early postoperative period was unremarkable in five patients. Patient 4 died from digestive bleeding 17 days after surgery, while patient 2 recovered from alveolar haemorrhage eight days post-transplantation. In patient 6, endomyocardial biopsy demonstrated recurrence of AL amyloidosis on the allograft four months after transplantation. Renal function progressed to end-stage renal failure in two patients: combined heart and kidney transplantation was performed in patient 7, while patient 1 received a kidney transplant 57 months after cardiac transplantation.

Following cardiac transplantation, four patients were given chemotherapy, after a mean period of 7.2 ± 3.6 months. Patient 5, who was untreated previously, received six courses of MD. Patients 1 and 2, who had been given MD before heart transplantation, received HDM/ASCT; MD therapy was reintroduced in both of these patients because of a lack of response to HDM/ASCT. Patient 6 was offered ABMT six months after surgery because of haematological relapse following HDM/ASCT in the pretransplantation period. Of these four patients, haematological response was not determined in one case (patient 1). Sustained complete haematological response was obtained with MD chemotherapy in patients 2 and 5. Patient 6, in whom a haematological response was not achieved following ABMT, died 50 months after heart transplantation from systemic amyloid progression and recurrence in the transplanted heart. Among the three patients who received only MD therapy prior to heart transplantation, complete free light chain response was maintained two years after MD in patient 8. In patients 3 and 7, the effect of chemotherapy was not assessed by

Table 3 Haematological therapy and response evaluation before and after heart transplantation.

| Patient	Extracardiac amyloid involvement	Haematological treatment	Response (sFLC)	Time (months)[a]	Transplantation	Haematological recurrence	Haematological treatment post-transplantation	Response (sFLC)
1	Kidney/liver	MD (3 courses)	ND	7	Heart then kidney	Yes	HDM/ACST then MD (2 months post-transplantation)	ND
2	Kidney/liver/nervous system[b]/pulmonary/skin/esophagus	MD (4 courses)	Partial	5	Heart	Yes	HDM/ACST then MD (10 months post-transplantation)	Complete
3	Nervous system[b]/skin	MD (4 courses)	ND	6	Heart	No	No	Partial
4	Nervous system[b]/kidney/liver/esophagus/skin	No	NA	2	Heart	NA	No	Progression
5	Kidney/nervous system[b]/skin	No	NA	3	Heart	NA	MD (6 courses) (11 months post-transplantation)	Complete
6	Nervous system[b]/liver/skin	HDM/ASCT	ND	27	Heart	Yes	ABMT (6 months post-transplantation)	Progression
7	Kidney/skin/esophagus	MD (4 courses)	ND	9	Heart and kidney	No	No	Complete
8	Kidney/skin/nervous system[b]	MD (6 courses)	Complete	6	Heart	No	No	Complete

NA: not applicable.
[a] Time from amyloid diagnosis to heart transplantation.
[b] Peripheral and autonomic nervous system.

Table 4 Heart transplantation data.

Patient	Time (months)[a]	Transplantation (year)	Cold ischemia/CP bypass time (minutes)	Donor (sex, age, cause of death)	Rejection episodes: ISHLT grade	Recurrence of cardiac amyloidosis	Follow-up (months)
1	7	Heart then kidney (2002)	83/ND	Male, 35 years, CH	No	No	58
2	5	Heart (2006)	221/180	Male, 23 years, CH	No	No	11
3	6	Heart (2005)	195/42	Female, 54 years, CH	No	No	28
4	2	Heart (2006)	148/108	Female, 53 years, CH	ND	ND	1.5 (death)[a]
5	3	Heart (2005)	202/123	Female, 49 years, CH	Yes: 3A (7 months post-transplantation)	No	23
6	27	Heart (2001)	180/58	Female, 32 years, CH	No	Yes	50 (death)
7	9	Heart and kidney (2005)	257/186	Female, 22 years, CH	Yes: 1B (8 months post-transplantation)	No	27
8	6	Heart (2005)	190/68	Male, 46 years, CH	No	No	25

CH: cerebral haemorrhage; CP: cardiopulmonary.
[a] Time from amyloid diagnosis to heart transplantation.
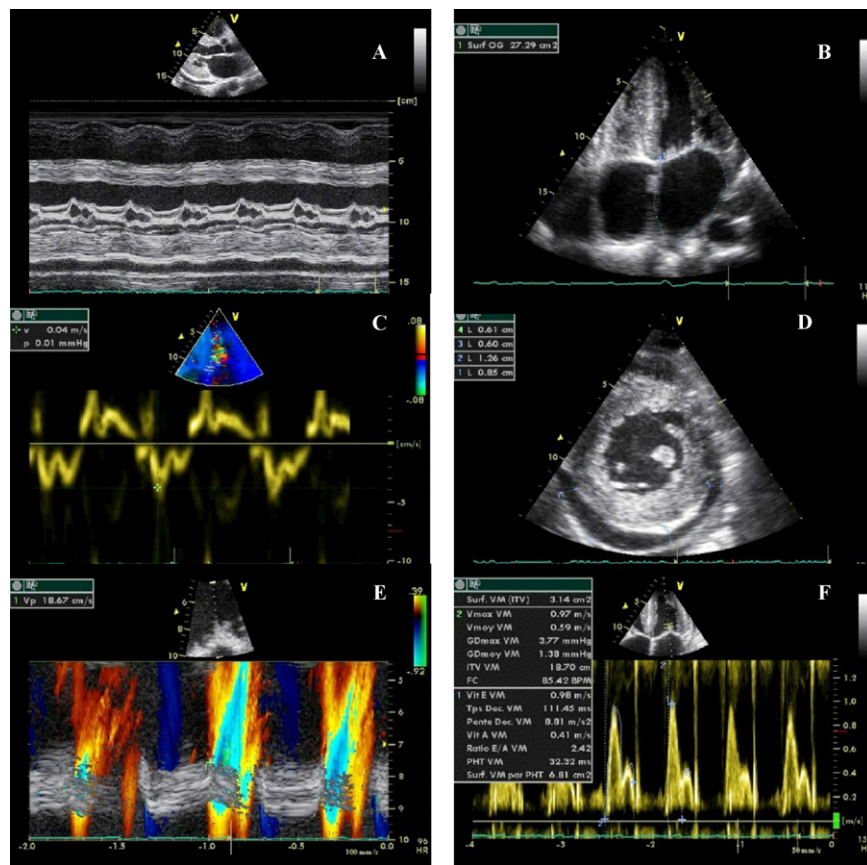
Figure 1. Pretransplant echocardiographic data (patient 8). A. Parasternal long-axis view. Increased echogenicity of the myocardium and valves, with pericardial effusion. Low mitral and aortic outflow. B. Apical 4-chamber view. Normal biventricular dimensions and biatrial enlargement. Concentric left ventricular and atrial septum thickening. C. Tissue Doppler imaging recorded from the lateral mitral annulus. Reduced myocardial velocity throughout systole and both phases of diastole, compatible with restrictive cardiomyopathy. D. Parasternal short-axis view. Concentric left ventricular thickening and small pericardial effusion. E. Apical 4-chamber view. Colour M-mode Doppler recorded from the mitral annulus: low flow propagation velocity across the cavity of the left ventricular. F. Apical 4-chamber view. Transmitral Doppler flow. Restrictive pattern with a short deceleration time and reduced A-wave velocity.

serum free light chain measurements. However, in patient 7, serum kappa to lambda ratio was within the normal range (0.64) at 27 months post-cardiac transplantation, indicating complete hematological remission. In patient 3, despite abnormal serum levels of free lambda light chains (423 mg/l, with kappa to lambda ratio of 0.02), the patient remained in good clinical condition after 28 months post transplantation. None of these three patients had evidence of recurrent amyloid deposits on the allograft.

After a median follow-up of 26 months, two patients had died; the clinical condition was good in the six remaining patients, without evidence of systemic amyloid progression
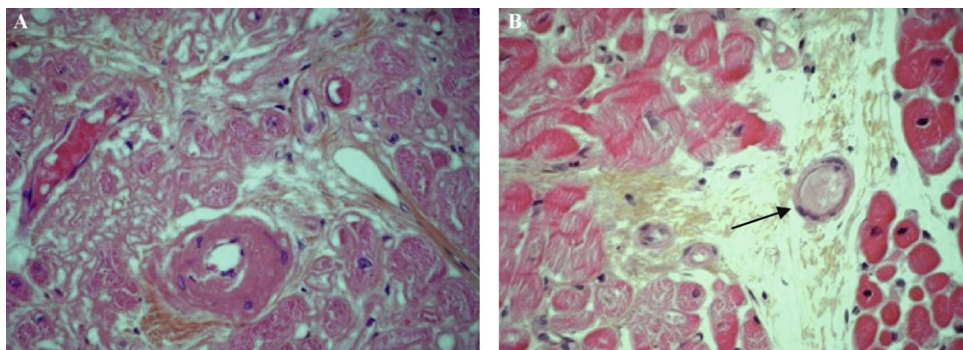
Figure 2. Endomyocardial biopsy before and after heart transplantation (patient 8). A. Endomyocardial biopsy of the explanted heart. Light microscopy, periodic acid-Schiff (PAS) staining, original magnification x 400. Parietal amorphous oeosinophilic deposits in a small myocardial artery. B. Graft endomyocardial biopsy, 2 years post-transplant. Light microscopy, PAS staining, original magnification x 400. No amyloid deposits were detected in myocardial interstitium and arteries (arrow). Mild infiltration by mononuclear cells.
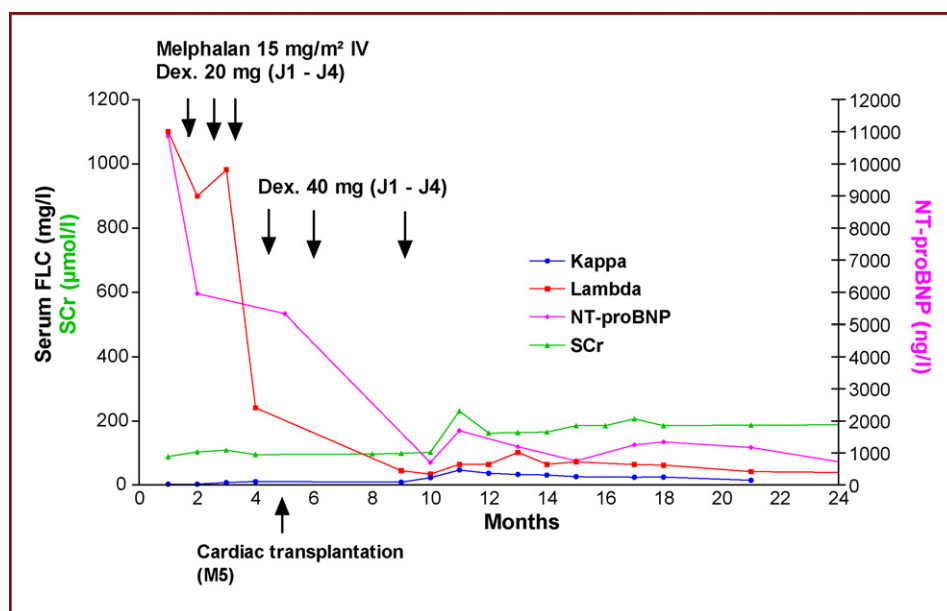
Figure 3. Follow-up of main biological parameters before and after heart transplantation (patient 8). FLC: free light chain; SCr: serum creatinine; Dex: dexamethasone.

or recurrence in the transplanted heart, as demonstrated by routine follow-up endomyocardial biopsies (Fig. 2, Table 4) (Fig. 3).

Discussion

Regardless of the nature of the amyloid precursor, cardiac amyloidosis is characterized by extracellular amyloid infiltration throughout the heart, with deposits involving ventricles, atria, valves, and intracardiac vessels. The infiltrative process results in biventricular wall thickening with non-dilated ventricles [2].

Typically, patients with heart failure resulting from AL amyloidosis present with rapidly progressive dyspnoea, almost always associated with evidence of elevated right-sided filling pressure on echocardiography. Fluid retention, which manifests initially as peripheral oedema, may be severe, particularly in patients with associated renal involvement. In the present study, seven of the eight patients had NYHA class 3 heart failure at the time of diagnosis of AL amyloidosis. Additionally, six patients showed typical electrocardiographic changes including diffuse low voltage, and or poor R-wave progression in the precordials leads mimicking myocardial infarction.

NT-proBNP is a sensitive marker of myocardial dysfunction that has been shown recently to be a prognostic factor in AL amyloidosis. Palladini et al. showed that a simultaneous reduction in amyloidogenic free LC and NT-proBNP levels with chemotherapy was associated with rapid improvement in cardiac function and prolonged survival. Interestingly, changes in NT-proBNP concentrations and cardiac function were not accompanied by significant changes in the amount of cardiac deposits, as evaluated by echocardiography. The authors suggested that myocardial dysfunction in AL amyloidosis could be related not only to the accumulation of amyloid deposits but also to direct cardiac toxicity exerted

by critical concentrations of the amyloidogenic precursor [16]. Unfortunately, BNP or NT-proBNP levels were measured in only three patients in the present study. In patient 8, a simultaneous reduction in lambda light chain and NT-proBNP levels with MD chemotherapy was associated with prolonged survival after heart transplantation. Altogether, these data suggest that serial measurements of NT-proBNP levels should be systematically performed in patients with AL amyloidosis to detect early cardiac involvement or recurrence on the allograft, and to evaluate the effect of treatment.

Doppler echocardiography is a key step in the diagnosis of cardiac amyloidosis. The echocardiographic appearance of advanced cardiac AL amyloidosis is characteristic, with non-dilated ventricles, concentric left and right ventricular thickening, prominent valves, and infiltration of the atrial septum. The myocardial texture is abnormal, with increased echogenicity of the myocardium and the valves, referred to as a ''granular sparkling'' pattern. Right ventricular free wall thickening, in the absence of pulmonary or systemic hypertension, strongly suggests myocardial infarction, which should be confirmed and identified by endomyocardial biopsy. In advanced disease, Doppler echocardiography typically shows a restrictive transmitral flow pattern, characterized by a short E wave deceleration time and a low velocity A wave. The decreased transmitral A wave in AL amyloidosis is not only related to endstage restrictive cardiomyopathy, but also to atrial amyloid infiltration. The LVEF is normal until late in the disease; when altered, it correlates with a significant reduction in short-term survival [2]. In the early stages of amyloid cardiomyopathy, the diagnosis may be challenging, as Doppler features depend on the stage of the disease, with diastolic dysfunction that progresses with myocardial infiltration [2]. As mild degrees of diastolic dysfunction are common among patients aged 50 years and older, this should not be used in isolation to diagnose cardiac amyloidosis. According to the consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis,

the echocardiographic criterion for the diagnosis of cardiac amyloidosis is a mean left ventricular wall thickness (septum and posterior wall) greater than 12 mm, in the absence of hypertension or other causes of left ventricular hypertrophy [15]. In the present study, this criterion was present in all seven patients, in whom echocardiographic findings were available for review, together with features of diffuse hypertrophic cardiomyopathy and diastolic dysfunction (Table 2).

Despite limited experience, there is growing evidence that cardiac transplantation may be life-saving in selected patients with end-stage amyloid heart disease. However, in systemic AL amyloidosis, both the criteria for eligibility for the procedure and the role of adjuvant therapies, aimed at controlling the underlying plasma cell disorder to prevent recurrence of amyloid deposits on the allograft and systemic progression of the disease, remain controversial. Since the first description of successful Cardiac transplantation in AL amyloidosis [4], only small multicentric series or case reports have been published [5—13]. Recently, in a retrospective analysis of the United Network for Organ Sharing (UNOS) database, Kpodonu et al. found that the actuarial one and five-year survival rates of all reported patients grafted for amyloid cardiomyopathy were significantly lower, compared to those with other cardiac conditions (74.6% and 54% versus 81.6% and 63.8%, respectively) [8]. Heart recipients with AL amyloidosis are at higher risk compared to those transplanted for other causes of amyloid cardiopathy, such as transthyretin or apolipoprotein AL amyloidosis. In seven patients with non-AL amyloid cardiomyopathy, Dubrey et al. reported survival rates of 86, 86, and 64% at one, two, and five years, respectively. By contrast, survival was 71, 71, and 36% at one, two, and five years, respectively, in seven AL amyloid patients who received post-transplant chemotherapy. In ten patients with AL amyloidosis who underwent transplantation but did not have additional chemotherapy, survival was only 50, 50, and 20%, respectively, with amyloid recurrence in the graft after a median of 11 months. If both perioperative mortality and incidence of allograft acute rejection were not significantly different compared to patients with non-AL amyloidosis, progressive extracardiac accumulation of deposits after cardiac transplantation contributed to mortality in 70% of AL amyloid patients [9]. Thus, severity of extracardiac amyloid organ involvement and its progression related to persistent production of amyloid-forming monoclonal light chains are major risk factors for mortality after heart transplantation in AL amyloidosis patients. The achievement of haematological remission appears to be a crucial point in the management of these patients.

Serial measurements of sFLC levels, which are abnormal in up to 98% of patients with AL amyloidosis, are mandatory for the evaluation of the haematological response after chemotherapy. Sustained suppression of clonal disease, as demonstrated by normalization or greater than 80% reduction in sFLC levels, is associated with prolonged survival [16—18]. In the present study, haematological response was evaluated monthly using the free light chain assay in only four of the eight patients. In patient 8, achievement of a complete clonal response, as demonstrated by a more than 80% reduction in sFLC levels, was a strong argument for the indication of cardiac transplantation, despite severe systemic disease.

In recent years, the overall prognosis of AL amyloidosis has been transformed with the use of new therapies such as HDM followed by ASCT. Although this approach is effective in controlling the source of amyloidogenic LC and inducing improvement in organ function and survival, the indications for HDM/ASCT are limited by high treatment-related mortality in patients with multiple organ involvement [14]. Substantial survival benefit from sequential heart transplantation and HDM/ASCT in AL amyloidosis was demonstrated recently by Gillmore et al., in five patients selected carefully for the absence of clinically significant extracardiac amyloid. HDM/ASCT was performed with a median time of 13 months from heart transplantation, as first-line chemotherapy in four cases. This approach resulted in prolonged survival times of 91.1 and 76.4 months from heart transplantation and HDM/ASCT, respectively. Three patients with sustained suppression of clonal disease (as demonstrated by normalization or greater than 80% reduction in sFLC levels), had a normal performance status and no evidence of cardiac or extracardiac amyloid accumulation after a mean follow-up period of 99 months from diagnosis. By contrast, death related to systemic and cardiac amyloid accumulation occurred in the two patients, in whom plasma cell dyscrasia failed to respond or relapsed after HDM/ASCT [10]. Recently, Sack et al. reported encouraging results in a series of seven patients transplanted for AL amyloid cardiac disease. With the exception of one patient who died from infection 201 days after the procedure, all patients survived the procedure and were free of cardiac symptoms. Chemotherapy was performed after cardiac transplantation in five patients, followed by HDM/ASCT in one case, which resulted in haematological remission in four patients (with normalization of sFLC levels in three patients); no patient had evidence of amyloid recurrence on the allograft. However, the chemotherapy protocols used in this study were not detailed [11].

Owing to the systemic nature of the disease, only a minority of patients with AL amyloidosis are eligible for sequential heart transplantation and high-dose chemotherapy [19]. In the present series, five patients received MD before heart transplantation because of the presence of significant symptomatic extracardiac manifestations, which were associated with a prohibitive risk of toxicity from the tandem approach. The MD combination is an effective therapy in AL amyloidosis. In a study of 46 patients who were ineligible for HDM/ASCT, 67% had a partial haematological response and 33% a complete response with this regimen (melphalan 0.22 mg/kg and dexamethasone 40 mg given orally on days one to four every 28 days). Reduction in the monoclonal component was associated with improved function of the involved organ in 48% of patients, resulting in a significant survival benefit. The short time to haematological response (median 4.5 months) probably accounted for these favourable results in patients with advanced disease [20]. Recently, in a randomized controlled trial involving 100 patients with systemic AL amyloidosis, MD resulted in improved overall survival compared with HDM/ASCT [21]. The present study also suggests that HDM/ASCT, which was performed as first-line therapy in one patient, and as rescue therapy in two patients, does not show improved efficacy over MD therapy in AL amyloidosis patients requiring cardiac transplantation.

In conclusion, heart transplantation may be associated with prolonged survival in AL amyloidosis heart disease, which remains largely under-diagnosed despite established criteria. Prognosis appears to be related closely to the achievement of clonal response with haematological therapy, either before or after surgery. The effect of treatment on the production of amyloidogenic monoclonal LC should be monitored carefully using sensitive techniques. For patients ineligible for HDM/ASCT because of significant extracardiac organ involvement, conventional chemotherapy with MD appears to be a promising alternative. Close collaboration between physicians involved in the care of this rare disease should improve the overall prognosis of cardiac transplantation in patients with AL amyloidosis.

Funding

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