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Improved outcomes after heart transplantation for cardiac amyloidosis in the modern era

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BACKGROUND: Cardiac amyloidosis, caused most commonly by deposition of light chain (AL) or transthyretin (ATTR) type fibrils, has an extremely poor prognosis. In this retrospective single-center study, we evaluated temporal trends in survival after heart transplantation for cardiac amyloidosis.

METHODS: We analyzed 48 patients with cardiac amyloidosis (AL, $n = 32$; familial ATTR, $n = 16$) who underwent heart transplantation from May 2002 to March 2017. Patients were analysed in 2 periods, Era 1 (2002– 2007) and Era 2 (2008– 2017), separated by altered patient selection in both, AL and ATTR amyloidosis, and changed chemotherapy regimens for AL amyloidosis.

RESULTS: The modern era was characterized by a lower number of extracardiac organ involvement for AL (94% isolated cardiac amyloidosis in Era 2 vs 56% in Era 1; $p = 0.0221$), and more frequent treatment for AL with the proteasome inhibitor bortezomib (94% in Era 2 vs 6% in Era 1; $p < 0.0001$). AL patients had significantly lower survival than patients with non-amyloid cardiomyopathy after heart transplantation in Era 1, and ATTR patients had numerically lower survival. However, survival in the modern era was comparable to non-amyloid transplants in both cohorts, possibly reflecting a shift in chemotherapy strategies and patient selection, respectively.

CONCLUSIONS: In the current era, use of enhanced chemotherapy regimens for isolated advanced AL cardiac amyloidosis was associated with outcomes comparable to non-amyloid cardiomyopathy. We conclude that heart transplantation in highly selected patients with isolated non-systemic advanced cardiac amyloidosis may be a feasible approach.

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Amyloidosis is triggered by abnormal extracellular deposition of low-molecular-weight fibrils, and the most common cardiac amyloidosis forms are light-chain (AL) and transthyretin (ATTR) amyloidosis.[1] AL amyloidosis is caused by plasma cell dyscrasia and monoclonal immunoglobulin light chains,[2] whereas ATTR amyloidosis is

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triggered by wild-type or genetically mutated transthyretin protein.[1] Cardiac amyloidosis is a rare disease but has a high clinical relevance as a result of common cardiac involvement with severe heart failure (> 50% of patients), associated high morbidity and an often fatal course.[3–6]

Currently, there are no conventional heart failure treatments, including pharmacologic approaches and device therapies, that have been shown to improve outcomes in these patients.[7–10] Therapeutic options are thus very limited, and advanced heart failure often prevents intensive chemotherapy and/or autologous stem cell transplantation (ASCT).[1,11,12] A few centers worldwide have pursued heart transplantation to allow causal treatments in advanced amyloidosis.[8,9,13–15] However, the results published are inconsistent. Some centers have reported high mortality, contrary to more recent publications with rather restrictive patient selection that showed more encouraging results.[8,9,13–21] Given the limited supply of donor hearts, heart transplantation in amyloidosis is still controversial, and many centers consider amyloidosis as a contraindication for this treatment approach.[16]

However, the effect of restrictive patient selection regarding organ involvement as well as modern therapeutic approaches for AL amyloidosis have so far not been elucidated in a larger cohort of patients with cardiac amyloidosis and heart transplantation. Our purpose was to evaluate outcomes in AL and familial ATTR amyloidosis in the modern era.

Methods

Between May 2002 and March 2017, 48 patients diagnosed with cardiac amyloidosis received heart transplantation at our center. Because prognosis is poor in these patients and the standard high-urgency criteria are not applicable to amyloidosis patients, we applied for an exceptional high-urgency status at Eurotransplant International Foundation for most patients. Between 2002 and 2007, 1 AL patient and 3 ATTR patients received transplants on the normal-urgency tier. All other patients received transplants on high-urgency status. Informed consent was given from all patients.

Data were analysed in a retrospective approach and separated in 2 periods: Era 1 (2002–2007) and Era 2 (2008–2017), marked by a more stringent patient selection regarding extra-cardiac organ involvement and an improved hematologic therapy for AL amyloidosis in Era 2. Survival of the patients with AL or ATTR amyloidosis after heart transplantation, censored on March 15, 2017, was compared with survival of patients who received a transplant at our center for common non-amyloid etiologies of end-stage heart failure under high-urgency status in the same time periods.

All patients underwent our institution's standard amyloidosis evaluation, including Congo-red staining and immunohistochemistry for typing of amyloid as well as free-light chain assay and, finally, molecular genetic testing in patients with ATTR amyloidosis. Cardiac amyloidosis was confirmed by immunohistochemical staining, and all patients showed advanced symptomatic cardiac amyloidosis with expected excessive short-term mortality risk. Evidence of light chain response to pre-heart transplant chemotherapy in AL patients was not necessary for eligibility, although it was generally considered as a favorable characteristic when candidacy was assessed.

Organ involvement was diagnosed and defined as previously recommended.[22] For instance, this included a positive renal tissue sample and proteinuria for kidney involvement, hepatomegalia, elevated alkaline phosphatase for liver involvement, and interstitial radiographic pattern and direct biopsy specimen verification for lung involvement. Mainly in Era 2, extracardiac organ involvement was an exclusion criterion for heart transplantation. Macroglossia, coagulation disturbance, and solely histologic proof of gastrointestinal involvement without symptoms were not counted as a contraindication for listing.

Further exclusion criteria for heart transplantation according to the DANGER criteria published by our group in 2009[13] were applied in Era 2: patients with diarrhea (D; weight loss, malabsorption), signs of autonomic (A) nervous system involvement (decreased heart rate variability, syncopes, polyneuropathy), impaired nutritional (N) status (assessed by serum protein, body mass index), gastrointestinal (G) tract involvement (history of gastrointestinal bleeding, gut biopsy), impaired elimination (E; renal function; nephrotic syndrome, increased creatinine), and respiratory (R) tract involvement (spirometry, diffusion capacity, computed tomography) were excluded from heart transplantation. Eligibility and listing for heart transplantation were determined for every patient by consensus of the Heidelberg heart transplant conference in conjunction with the Heidelberg amyloidosis center team. A detailed further description of methods and statistics is available in the expanded Supplementary Material (available online at www.jhltonline.org).

Results

Baseline characteristics

Between 2002 and early 2017, 48 patients, 26 men (54%) and 22 women (46%), with cardiac amyloidosis underwent heart transplantation at the University of Heidelberg; of these, 32 (67%) had AL and 16 (33%) had familial ATTR amyloidosis. The median age at the time of heart transplantation was 55 years (25th–75th percentile, 49–58 years). In the non-amyloid group of high-urgency transplant patients that was used for the comparison of post-transplant survival, age at heart transplantation was comparable (54 years; 25th–75th percentile, 44–59 years), whereas sex distribution was significantly shifted toward male sex in the non-amyloid group (80% male vs 20% female; $p < 0.001$ vs amyloidosis patients).

Tables 1 to 5 give the data separated for AL and ATTR amyloidosis and separated for the 2 eras. Detailed baseline characteristics of the study population are summarized in Table 1. Importantly, patient selection was more stringent in Era 2. This was reflected by, for example, a significant reduction in proteinuria in the AL group in Era 2 (Table 1). Further characterization of the groups is given in Table 5 (AL subtype), Supplementary Table S1 (pre-transplant chemotherapy and ASCT for light chain (AL] amyloidosis, online), and Supplementary Table S2 (ATTR genotypes, online). Taken together, the baseline characterization revealed that fewer organs were involved in AL amyloidosis in Era 2 (94% isolated cardiac amyloidosis) than in Era 1 (56%; $p = 0.0221$). Although we did not find a statistical significance for the ATTR group ($p = 0.1241$), we also observed a higher number of patients with only cardiac involvement in Era 2