Heart transplantation in cardiac amyloidosis

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Abstract

It is known that the prognosis of patients affected by light-chain (AL) or transthyretin-related (TTR) amyloidosis is poor. TTR amyloidosis has usually shown a slower progression than AL amyloidosis, both hereditary TTR amyloidosis, where there is an inherited mutation in the DNA, and wild-type TTR amyloidosis, which usually affects the elderly. In this paper, the current literature about heart transplantation on cardiac amyloidosis patients is extensively reviewed. The two most frequent types of cardiac amyloidosis have been considered for heart transplantation: AL amyloidosis and wild-type TTR amyloidosis. According to this analysis, it is reasonable that heart transplantation may represent a valuable option in carefully selected patients. Moreover, it could improve prognosis, enabling autologous stem cell transplantation in the AL amyloidosis subgroup. In our humble opinion, it is mandatory to define a multidisciplinary approach to help select candidates to obtain the most effective results.

Keywords: Heart transplantation, cardiac amyloidosis, prognosis

INTRODUCTION

Heart transplantation (HTx) is the leading option for advanced heart failure (HF) patients; however, some issues must be considered when HF is secondary to systemic diseases with predominant heart involvement. Thus, screening for HTx involves a complete screening to exclude important co-pathologies that can worsen the short-term outcome or the long-term survival.
Cardiac amyloidosis (CA) is a systemic disease due to the aggregation of amyloid fibrils that commonly deposit in the renal, cardiac, and hepatic tissues, as well as the peripheral and autonomic nervous systems\(^1\). Restrictive cardiomyopathy is the worst manifestation of CA, and it is present in 20% of symptomatic patients at diagnosis\(^2\). There are different variants that involve the heart: primary (AL) amyloidosis and familial (TTR) amyloidosis are the most common forms\(^3-5\).

AL amyloidosis is due to the clonal production and deposition of immunoglobulin light chains, and this phenomenon leads to an underlying plasma cell dyscrasia. For this reason, the most effective cyto-reduction therapy is high-dose chemotherapy, followed by autologous stem cell transplantation (ASCT)\(^6-7\). However, when patients show severe heart impairment, they are not candidates for ASCT due to the high risk of mortality, thus having a median survival not longer than nine months\(^8\). Recent studies have revealed that, in more than 40% of cases, CA is diagnosed with a long delay\(^9-10\). This point could justify the high number (~30%) of patients with severe and advanced organ involvement and the relatively early death after diagnosis\(^11\).

ATTR amyloidosis usually has a slower progression than AL amyloidosis. Transthyretin is a hepatic protein with carrier function. In ATTR, the protein deposits in the heart and/or the nerves and other organs and tissues. There are two forms of ATTR amyloidosis: hereditary ATTR amyloidosis, where there is an inherited mutation in the DNA, and wild-type ATTR amyloidosis, which usually affects the elderly\(^12\).

Recent studies have reported satisfying results for the treatment of wild-type ATTR amyloidosis using new molecules, such as tafamidis. Effectively, patients initially treated with tafamidis had better survival than placebo, leading to the approbation of this drug in several countries\(^13\).

**BACKGROUND**

Patients’ survival in amyloidosis is extremely heterogeneous: patients without heart involvement can survive some years; conversely, most patients with advanced cardiac damage die early\(^13\). Historically, cardiac transplantation was a contraindication in AL-CA. Only recently has it been described in AL amyloidosis patients\(^14\). At that time, few case reports showed that outcomes at short and medium-term were similar to those in other diseases\(^14-17\); conversely, larger case series showed worst results compared to the patients transplanted for other cardiomyopathies\(^14\). Thus, patients affected by AL-CA were excluded for HTx for all these reasons.

The real revolution in this approach came when it was standardized that AL-CA patients needed to be treated with high-dose melphalan followed by ASCT after HTx to suppress the production of monoclonal light chains\(^19\). Of note, this strategy of treating patients after HTx allowed reaching a complete hematologic response one year after treatment in 40% of patients with primary AL amyloidosis\(^20\). Since cardiac transplantation for amyloidosis is not common, the studies available are generally small and based on single-center experience\(^21\) [Table 1]. Moreover, other difficulties in comparing studies are related to the variability of follow-up lengths, the patient selection criteria, and the different concurrent treatments.

Concerning the ATTR CA patients, the first proposed option was liver transplant (LT); subsequently, HTx has been combined with LT to avoid the potential development of the cardiomyopathy after LT alone\(^22-23\). Conversely, isolated HTx has been done in those patients without extracardiac deposits and end-stage HF, showing very encouraging results\(^24\). Considering all these premises, the International Society of Heart and Lung Transplantation has recently assigned a class IIA recommendation for HTx in CA patients\(^25\).
Table 1. The relevant results in HTx patients affected by AL and ATTR amyloidosis

| N of patients | AL/ATTR | Comments |
|---------------|---------|----------|
| 23            | AL      | Five-year survival of 43% vs. 85% for non-amyloid patients |
| 7             | ATTR wt | One-non-amyloid-related death |
| 31            | 13 AL   | 18 ATTR  | No differences in survival |
| 8             | AL      | 75% alive (2.2 years of follow-up) |
| 12            | NA      | One- and three-year survival rates similar to non-amyloid transplant patients |
| 48            | 32 AL   | 16 ATTR  | Median survival of 61% after 3.5 years |

HTx: Heart transplantation. AL: light-chain.

Heart Transplantation in AL Amyloidosis

The introduction of ASCT after HTx in AL CA patients has changed the scenario of HTx availability in this subgroup of patients. The first experiences were limited to a few cases. Roig et al. [26] reported sequential HTx/ASCT in five patients with AL cardiac amyloidosis: 2/5 died from progressive amyloidosis and 3/5 are alive, including one who developed progressive plasma cell dyscrasia that was successfully treated with high-dose corticosteroids. Lacy et al. [27] from the Mayo Clinic published a series of 11 patients undergoing sequential HTx/ASCT, reporting that 2/11 patients died from transplant-related toxicity and 3/11 died from progressive amyloidosis. The largest series of patients transplanted for CA was published in June 2021 from the United Network for Organ Sharing registry from 1987 to 2018, where the authors reported 313 patients affected by CA who underwent isolated HTx, with encouraging results [28].

Italian data

For the first time in Italy, some data on HTx in CA patients were published, showing that sequential HTx-ASCT is feasible and assuring a good survival in highly selected AL CA patients, with satisfactory early and late outcomes [29]. Thus, in this paper, 36 amyloidosis patients are included from 2009 to 2019. Of these, nine had cardiac involvement, 7/9 due to AL amyloidosis and 2/9 due to wild-type TTR amyloidosis. All were survivors during the wait for HTx. ASCT was performed in 6/7 AL CA patients, with a median time of six months after HTx. Survival was 88% and 66% at one and five years, respectively.

Satisfying results in this peculiar disease could be reached only with specific follow-up programs after HTx-ASCT to anticipate the potential manifestations of CA over time [26]. Accordingly, some different consensus criteria have been defined [30]. Patients who have a total remission of the disease with no evidence of monoclonal immunoglobulins in serum or urine and normal serum free light chains reach the best results. Conversely, a partial response consistent in a reduction of 50% or more in concentrations of aberrant free light chains is not satisfactory [31]. It is known that renal dysfunction and gastrointestinal amyloid involvement may be associated with a worse prognosis and a higher rate of complications after ASCT [32]. For these reasons, it is mandatory to deeply evaluate all candidates for any gastrointestinal, hepatic, or renal involvement, including severe neuropathy or coagulopathy.

Another crucial point in this setting is related to the time of ASCT after HTx. Lacy et al. [27] suggested to pursue ASCT in a time near to six months after HTx: sooner it may be difficult if the patient continues to require intensive immunosuppression, and later it may be too late for the risk of amyloidosis progression in other organs. This time-control strategy between HTx and ASCT could be another point of improvement in the survival of amyloidotic patients after HTx, in contrast to the previous analysis [33].
Heart Transplantation in TTR Amyloidosis

The decision to proceed with heart transplantation in ATTR might be different in wild-type vs. variant ATTR amyloidosis. Thus, patients affected by variant ATTR amyloidosis are younger than those with wild-type ATTR and might benefit from heart transplantation after careful candidate selection. Moreover, patients with ATTR variant showed increased cardiac tropism, which is known to heavily infiltrate the native heart early in the disease course. For these reasons, variant ATTR amyloidosis patients should be regularly investigated to identify the best frame for heart transplantation according to NYHA class, NT-proBNP, systolic and diastolic function, CPET parameters, RM parameters, and extra-cardiac organ function\textsuperscript{34-36}.

Patients with wild-type TTR amyloidosis and isolated cardiac involvement should be considered for HTx, and the data available suggest that post-transplant prognosis for this subgroup of patients is comparable to that of transplantation for other reasons. ATTR amyloidosis is predominantly a disease of the elderly, and progression is usually slow; thus, it is reasonable that it could be too slow to significantly damage the transplanted heart. However, knowing that age is a limit in the donor organ offers, ATTR amyloidosis is a rare indication for cardiac transplant, and the number of cases reported in the literature is small. In a group of seven patients with wild-type TTR with HTx between 2007 and 2015, the three-year survival was 100%, and the one death was due to a neoplastic reason\textsuperscript{24}. However, symptomatic gastrointestinal and peripheral nerve involvement by wild-type ATTR developed subsequently. In another series, two patients with wild-type ATTR amyloidosis were transplanted in 2012 and 2017, respectively, and they are in good clinical conditions, without relapse of amyloidosis in the donor grafts\textsuperscript{29}. Before the recent news about new drugs for this disease with good results\textsuperscript{37}, HTx has offered the greatest chance of long-term survival for wild-type ATTR amyloidosis patients; however, a change in the therapeutical approach is already ongoing after the latest evidence\textsuperscript{38}, leading to HTx having a marginal role in this subgroup of patients.

Open issues in HTx for cardiac amyloidosis

Some open issues related to the referral of systemic disease patients for HTx are largely debated. Effectively, with the limited number of donors, public scrutiny of the HTx results, and apparent inferior survival in amyloidosis patients compared to transplant recipients for other causes, only large programs can afford to take the risk of performing cardiac transplants in CA. Moreover, being unquestionable that outcomes in AL amyloidosis are better after chemotherapy and ASCT, the number of transplant centers is further limited to those where there are close cooperating programs between the transplant and the cancer centers and that are used with ASCT. Effectively, transplant hospitals always struggle with the option of guaranteeing a very rare resource to patients with a systemic and progressive disease\textsuperscript{39-41}, but the choice of having extended marginal donors could be a chance, trying to afford this ethical dilemma\textsuperscript{42}. The option of using extended donor criteria for these recipients\textsuperscript{41} supports the ethical question of whether transplantation is an option in these patients besides the shortage of donor organs.

Another crucial point is related to the criteria adopted to exclude these patients from HTx programs. According to the DANGER protocol published in 2009, patients showing diarrhea (D: such as weight loss or malabsorption), autonomic nervous system (A: heart rate variability and synapses), nutritional status (N: decline of serum protein or weight), gastrointestinal tract involvement (G: gut biopsy or known gastrointestinal bleeding), impaired elimination (E: kidney function), and respiratory tract involvement (R: evaluated by spirometry and computed tomography) are not considered for HTx\textsuperscript{41}. Hence, the choice of transplanting these patients must be considered according to a case-by-case evaluation [Table 2]. As for all patients, HTx candidates should be evaluated for their general conditions, as survival is critically dependent on different patient characteristics, such as extra-cardiac amyloid deposits and patient age\textsuperscript{41}. Lastly, a surveillance protocol based on monthly or three-monthly evaluations is necessary to monitor and prevent
Table 2. Specific examinations needed before candidacy to HTx

| Specialistic evaluation | Routine lab tests/physical investigation |
|-------------------------|------------------------------------------|
| Renal                   | Proteinuria; count of light chains; Bence Jones proteins; urine protein electrophoresis; kidney biopsy in the case of suspected renal amyloidosis |
| Hematological           | Blood exams; serum protein electrophoresis; plasma cell counting; bone marrow biopsy with aspirate |
| Neurological            | Clinical investigation to confirm/exclude peripheral neuropathy |
| Gastrointestinal        | Clinical investigation; stool collection for fecal fat to rule out malabsorption; esophagogastroduodenoscopy and colonoscopy with biopsies to rule out amyloid deposits in the gastric and intestinal mucosa |

HTx: Heart transplantation.

Potential relapses of the disease, including routine cardiac biopsy investigations of the donor’s heart and effectively treating any unpleasant recurrences of amyloid infiltration in the graft.

CONCLUSIONS
Heart transplantation is an effective option in patients affected by cardiac amyloidosis, both AL and ATTR. Due to the rarity of the diagnosis, data available about HTx are scarce but encouraging. Concerning the typical multi-organ disorders, a multidisciplinary approach is highly suggested to choose the best candidates and reach the best long-term results. Moreover, anticipated referral to tertiary centers may be desirable to optimize the results at early- and long-term follow-up.

DECLARATIONS
Author’s Contributions
Conceiving the manuscript and writing: Di Nora C
Contribution and implementation of the design of the research: Sponga S
Collection of the data, analyzing the data: Nalli C
Collection of the data, analyzing the data: Driussi M
Performing heart surgeries: Vendramin I
Collection of the data, performing heart surgeries: Benedetti G
Collection of the data, performing heart surgeries: Guzzi G
Planning and supervision of the manuscript: Imazio M
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