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TITOLO TESI

**LIVER TRANSPLANTATION FOR TRANSTHYRETIN AMYLOIDOSIS:
EXPERIENCE OF A SINGLE CENTER IN ITALY.**

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Abbreviations: TTR = Transthyretin; LT = Liver Transplantation; HT = Heart Transplantation; mBMI = modified Body Mass Index; HR = Hazard Ratio; CI = confidence intervals.

ABSTRACT

Liver transplantation is the only definitive treatment for transthyretin amyloidosis, with an excellent 5-year survival in endemic countries where the Met30 mutation is predominant. We report our experience of liver transplantation for transthyretin amyloidosis. We reviewed the clinical records of 17 transplanted patients (11 males, 6 females; age at liver transplant: 45.7 ± 11.7 years).

We had a wide spectrum of non-Met30 mutations (52.9%), with a predominance of Gln89 (23.5%). Five-year survival after transplantation was 43.8%; at multivariate analysis, both non-Met30 mutations (HR 17.3, 95% CI 1.03-291.7) and modified BMI (HR 0.50, 95% CI 0.29-0.87) showed significant and independent prognostic roles ($P=0.048$ and $P=0.015$, respectively). Five out of the 9 non-Met30 carriers received combined heart transplantation because of severe cardiomyopathy; they showed a trend towards a better prognosis vs. the 4 patients who did not receive combined heart transplantation (although not statistically significant; $P=0.095$). At follow-up, no significant improvement of transthyretin amyloidosis manifestations was observed. The results of liver transplantation for transthyretin amyloidosis in our population are poorer than those reported in the literature probably because of the high prevalence of non-Met30 mutations.

BACKGROUND AND AIMS

Transthyretin (TTR) amyloidosis is an autosomal, late-onset disease, caused by the mutation of a single gene on chromosome 18 codifying for TTR, a tetrameric physiologic plasma protein. To date, more than 100 different amyloidogenic mutations have been reported (1); the substitution of valine by methionine at position 30 (Met30) is by far the most frequent, with well-known endemic foci in Portugal, Sweden and Japan. Amyloidogenic mutations destabilize the molecule, favouring tetramer dissociation, with the generation of unstable intermediates which are prone to precipitate and to self-aggregate into amyloid fibrils in tissues, impairing their structure and function.

Over 95% of the mutated protein is produced by the liver, and typically affects the peripheral nervous system and the heart, leading to disabling sensory-motor and autonomic neuropathy, arrhythmias, and restrictive cardiomyopathy. In the Met30 mutation, peripheral neuropathy dominates the clinical picture and death occurs 7 to 10 years after the onset of symptoms. In many rarer mutations, clinically relevant cardiac involvement, which is generally a late phenomenon among Met30 carriers, appears to be the predominant feature (2, 3, 4, 5, 6)

Furthermore, all the TTR variants can potentially be associated with mutated protein production by the choroid plexus and the vitreous (7) In this setting, we can observe, leptomeningeal, cerebrovascular and nerve root deposits with the risk of infarction or haemorrhage, and vitreal deposits with reduced vision reduction and glaucoma. Since leptomeningeal deposits and ocular involvement are frequently associated, these forms are referred to as familial leptomeningeal or oculoleptomeningeal amyloidosis (8, 9, 10, 11, 12, 13, 14, 15, 16, 17)

Currently, liver transplantation (LT), abolishing the supply of mutated protein, represents the only definitive treatment for TTR amyloidosis, with an excellent 5-year patient survival rate. However, a significantly lower survival rate has been reported in patients with non-Met30 mutations, mainly because of perioperative cardiac complications (18, 19). Moreover, progression of amyloidotic cardiomyopathy (20, 21, 22, 23) and progression or de novo

oculoleptomeningeal deposits after surgery (24) have been described. Vitreous deposits can easily be treated, while the issue of LT for leptomeningeal variants remains to be evaluated.

An interesting corollary of performing LT in patients with TTR amyloidosis is the possibility of using their removed liver for grafting into another patient with end-stage liver disease, a procedure called domino LT. The pending problem is the risk of de novo amyloidosis in the recipients of the amyloidotic liver; although, in the first series, none showed symptoms of the disease (18), a case of systemic TTR amyloidosis has recently been reported (25).

We herein report our experience of LT for TTR amyloidosis in a single Italian transplant center. Some of our cases have been previously reported as single case reports. The aim of the present study was to analyze the entire group of transplanted patients in order to assess patient survival and the relative prognostic factors. The secondary goals were to evaluate the course of the disease after LT and the results of domino LT.

PATIENTS AND METHODS

From May 1993 to May 2006, 17 patients underwent 18 LTs for TTR amyloidosis at our Institution, 5 of whom also received heart transplantation (HT). Their clinical records at the time of surgery were reviewed. In order to evaluate the course of the disease after LT, the same data were evaluated at the time of the last follow-up; a minimum follow-up of 6 months was considered suitable to detect clinical modifications.

Peripheral sensory-motor damage was classified into 4 stages: absent; mild sensory (thermo-dolorific) deficit limited to the lower limbs; global sensory loss extending to the upper limbs with motor involvement in lower limbs (distal muscle atrophy and steppage gait); unable to walk (bedridden or wheelchairbound). This scale was chosen because it has been specifically validated in amyloidotic patients (26). In order to assess nutritional status, we calculated the modified body mass index (mBMI), according to Suhr et al. (27, 28, 29). The presence of gastrointestinal symptoms, bladder dysfunction, orthostatic hypotension and erectile dysfunction in men were also evaluated in order to characterize the involvement of the autonomic nervous system.

Heart involvement was assessed by echocardiography and electrocardiography. The presence of amyloidotic cardiomyopathy was defined as end-diastolic thickness of the interventricular septum >12 mm (in the absence of any other cause of ventricular hypertrophy) plus two or more of the following: (a) homogeneous atrioventricular valve thickening, (b) atrial septal thickening and (c) sparkling appearance of the ventricular septum (30). The left ventricular mass, which was calculated according to the formula reported by Devereux et al. (31), was considered increased when >130 g/m² in men and >110 g/m² in women. An 'abnormal electrocardiogram' was defined according to the presence of one or more of the following features: conduction disturbances (right bundle branch block, left bundle branch block, left anterior hemiblock, atrioventricular block), low QRS voltage (QRS amplitude ≤ 0.5 mV in all limb leads or ≤ 1 mV in all precordial leads), ST and T wave abnormalities, and 'pseudoinfarction' pattern. Patients with echocardiographic signs of amyloidosis underwent endomyocardial biopsy, and the amounts of

amyloid deposits were semiquantitatively classified as mild (<30% involvement of the tissue fragments), moderate (30% to 60% involvement) or severe (>60% involvement) (32).

Five out of 17 harvested grafts from patients with TTR amyloidosis were used for sequential LT in 5 patients; the clinical data of the recipients of domino LT at the time of surgery and at the last follow-up were reviewed.

The study was conducted according to the principles of the Helsinki declaration. The data were collected in the course of routine clinical practice. Informed consent was obtained before the instrumental examinations according to the protocol of the institution which performed the evaluations.

Statistical analysis

Means, standard deviations, frequencies and ranges were used as descriptive statistics for the data; median follow-up times were also reported. The Fisher's exact, the Pearson and the linear-by-linear association chi-square, and the McNemar, the Mann-Whitney and the Wilcoxon tests were used to analyze the data. The cumulative proportion of surviving patients over time, as well as the mean survival times together with their 95% confidence intervals (95% CI) were estimated according to the Kaplan-Meier method. The univariate and multivariate Cox's proportional hazard regression model was used to identify predictors of survival and the hazard ratios (HRs) were reported together with their 95% CI. Two-tailed P values less than 0.05 were considered significant. Data were analyzed by means of the SPSS for Windows version 12.0.

RESULTS

Basal characteristics

In our population, we observed a low prevalence of patients with the Met30 mutation (8/17; 47.1%). Among mutations other than Met30, we had a predominance of the Gln89 variant (4/17; 23.5%); and one case each of the other non-Met30 mutations represented 29.4% (Ala49, Arg47, Leu68, Pro36, Thr34).

The characteristics of the 17 transplanted patients at the time of surgery are reported in Table 1. Combined HT-LT was performed in 5 patients, because of severe cardiomyopathy, which was symptomatic in 3 (NYHA 2-3). Four patients were carriers of Gln89 and 1 was a carrier of Leu68.

Survival

Eight out of 17 patients (47.1%) died after transplant. The overall 1-year and 5-year survival rates were 70.1% and 43.8%, respectively, with a mean survival of 6.4 years (95% CI 3.1-9.7 years).

Two patients with the Met30 mutation died from causes related neither to surgery nor to TTR amyloidosis: a 30-year-old male in a car crash and a 38-year-old female from colon cancer, 18 and 11 months after LT, respectively. The other 6 deaths were related to surgery or to the disease and some of them have previously been described. A brief description of these 6 cases follows. A 22-year-old female (Arg47) died during surgery from severe haemodynamic instability after graft reperfusion. The transplant operation had been complicated by rupture of the spleen, requiring a splenectomy; pathological examination of the spleen confirmed the presence of diffuse amyloid deposits (33). A 57-year-old male (Thr34), who received 2 LTs because of primary graft nonfunction, died 8 days after the second LT from cardiac complications; at basal myocardial biopsy, he had moderate myocardial damage. A 43-year-old female (Pro36) died 21 days after LT from massive subarachnoidal haemorrhage; histological examination of the brain showed amyloid deposition in the subarachnoid and subpial vessels (**Errore. Il segnalibro non è definito.**). A 54-year-old male (Gln89) died 2 months after combined HT-LT from sepsis and

multiorgan failure; in the postoperative period, he underwent 2 surgical operations for intrapericardial and abdominal bleeding (34). Finally, two males (a Gln89 45-year-old who also underwent HT, and a Met30 57-year-old) died 19 and 36 months after transplantation respectively from malabsorption. At the time of surgery, their mBMIs were 537 and 524, respectively.

Prognostic factors

In order to evaluate the factors affecting survival after LT for TTR amyloidosis, the follow-up of the 2 patients who died from causes related neither to surgery nor to the disease were considered censored at the time of death.

Analysis of survival by type of mutation showed that patients with non-Met30 variants seem to have a higher risk of death after LT as compared to those with the Met30. One- and 5-year survival rates were 55.6% and 37.0% for non-Met30 vs. 100% and 75.0% for Met30 patients respectively, with a mean survival of 2.8 years (95% CI 0.6-5.0) and 10.6 years (95% CI 6.3-15.0), respectively (HR 6.60, 95% CI 0.76-57.2; P=0.087) (Figure 1).

Among the 9 patients with non-Met30 variants, a tendency towards a better prognosis for patients who received combined HT was observed, although it was not statistically significant (HR 0.14, 95% CI 0.01-1.41; P=0.095); the 1-year survival rate was 80.0% for patients who received combined HT vs. 25.0% for patients who underwent LT alone.

Nutritional status was significantly correlated to patient survival after transplantation, with a significant reduction in the risk of death for each increase of 100 units in mBMI (HR 0.54, 95% CI 0.30-0.94) (P=0.031). Survival was significantly worse (HR 5.18, 95% CI 1.03-26.1; P=0.046) in the 3 patients with an mBMI <600: 66.7% and 0% at 1 and 5 years than in the 14 patients with an mBMI \geq 600: 78.6% at both 1 and 5 years. Mean survival was 1.5 years (95% CI 0.0-3.2) in the former group vs. 10.4 years (95% CI 7.6-13.2) in the latter group (Figure 2).

None of the other parameters showed a significant impact on survival after LT: duration of symptoms before LT (P=0.582), grade of peripheral nervous system involvement (P=0.074),

orthostatic hypotension ($P=0.280$), bladder dysfunction ($P=0.546$), age at transplantation ($P=1.000$), combined HT-LT ($P=0.996$) and end-diastolic thickness of the interventricular septum ($P=0.830$ in the 12 patients who did not receive HT).

At multivariate analysis, both non-Met30 mutations (HR 17.3, 95% CI 1.03-291.7) and mBMI (HR 0.50, 95% CI 0.29-0.87) showed a significant and independent prognostic impact on patient survival after transplantation ($P=0.048$ and $P=0.015$, respectively).

Course of the clinical manifestations of amyloidosis after transplant

The course of the clinical manifestations of amyloidosis was analysed in the 12 patients with a post-transplant follow-up ≥ 6 months. The median follow-up time after transplantation in this cohort was 2.2 years (range 0.9-13.2 years). The comparison of the clinical manifestations of amyloidosis at the end of the follow-up vs. the clinical manifestations at the time of transplant did not show a significant improvement of symptoms ($P=1.000$ for sensory-motor neuropathy, $P=0.241$ for mBMI, $P=1.000$ for orthostatic hypotension, $P=1.000$ for bladder dysfunction; McNemar and Wilcoxon tests).

Regarding heart involvement, at follow-up, none of the 4 patients who had received combined HT-LT (3 with Gln89 and 1 with Leu68 mutations) acquired evidence of amyloid deposition in the transplanted heart at the yearly echocardiographic and histological evaluation. None of the remaining 8 patients who had undergone LT alone (7 with Met30 mutation, 1 with Ala49 mutation) developed symptoms consistent with cardiac amyloidosis at follow-up. An echocardiogram, available in 4 of these 8 patients (all Met30), did not show a significant increase ($P=0.317$; Wilcoxon test) in end-diastolic thickness of the interventricular septum (14.5 ± 3.0 mm at pre-transplant and 15.3 ± 2.9 mm at follow-up).

Domino transplantation

We started to use sequential LT in May 2003; since then, 5 patients (2 males, 3 females) have received the harvested graft from patients with TTR amyloidosis (2 from Met30, 1 from Gln89, 1 from Ala49 and 1 from Leu68 carriers). The mean age of the recipients at surgery was 52.8 ± 12.8

years (range 33-64 yrs). Three patients underwent domino LT due to hepatocellular carcinoma from alcoholic (n=1) or viral cirrhosis (n=2), 1 due to HCV cirrhosis without cancer and 1 (a 33-year-old female) due to a cholangiocarcinoma. This last patient received domino LT after the loss of a previous living graft from her homozygote twin due to late hepatic artery thrombosis; she also had a chronic HCV infection.

The youngest patient (the 33-year-old female) died 17 months after domino LT from recurrent, cholestatic hepatitis C, in the absence of recurrent cholangiocarcinoma (20 months after the first LT). The other 4 patients are alive and in good condition. The median follow-up after domino LT is 1.2 years (range 0.2-3.2). None of the recipients of domino LT developed clinical evidence of amyloidosis at follow-up.

DISCUSSION

Today, LT is considered the only definitive treatment for TTR amyloidosis since over 95% of TTR is produced by the liver; the rationale for LT is to stop disease progression by abolishing the supply of mutated protein. The five-year patient survival rate after LT is reported to be 77% (18), which is comparable to the survival of LT performed for chronic liver disease. However, the majority of studies in the literature report data from endemic countries where the Met30 mutation is predominant while the real benefit of LT for patients with other variants is still less clear.

In our experience, the overall 5-year survival rate after LT was 43.8%. This value, which is notably below the average reported in the literature, probably depends on the higher prevalence of non-Met30 variants in our cohort of patients. In fact only 47.1% of our patients carried the Met30 mutation, compared to 83% in the Familial Amyloidotic World Transplant Registry (18). Our speculation is supported by multivariate analysis which revealed a significant and independent higher risk of death for non-Met30 carriers after having adjusted for the differences in mBMI.

Besides the TTR variant, mBMI was also significantly associated with post-LT survival at multivariate analysis. The risk of death decrease 50% for each 100 unit increase of the mBMI; these data are consistent with the literature (27, 28, 29) and suggest that patients should undergo LT early when their nutritional status is still good.

In our population 5 non-Met30 patients underwent combined LT-HT because of severe cardiac involvement. The rationale for such a policy was supported by the observations of an incremental surgical risks of LT in cardiomyopathic patients (19, 22), a poor prognostic impact of established severe cardiomyopathy in patients who survive LT (19), and the possibility of cardiomyopathy progression after LT alone (20, 21, 22, 23). Moreover, in our experience, even in non-transplanted patients, cardiac involvement is a major component of the phenotypic expression of non-Met30 TTR amyloidosis. In particular, the ominous prognosis of the Gln89 carriers appears

to be mainly due to cardiovascular events, irrespective of the degree of neurological impairment (6).

In our experience, HT combined with LT did not show a negative impact on survival and, at follow-up, none of these patients had evidence of amyloid deposition in the transplanted heart, confirming that this strategy is safe and effective for patients with heart involvement.

Another controversial issue is the true ability of LT to halt the progression of the disease. In our population, the symptoms of the disease stabilized in all patients after LT, but none of them showed a significant improvement thus suggesting that LT should be performed before the patient's functional status has been compromised.

In conclusion our experience although limited by the low number of patients, confirms an excellent patient survival in Met30 carriers and a significantly lower survival in other variants. Carriers of non-Met30 variants with amyloidotic cardiomyopathy should be carefully evaluated in order to decide the need for combined HT-LT suggesting that the treatment should be tailored to the variant. An mBMI below 600 has been confirmed to be one of the most important negative prognostic factor for patient survival, and should probably be considered an absolute contraindication to LT. The absence of clinical improvement after surgery confirms that, when indicated, LT should be performed early in the course of the disease to improve survival and to ensure an acceptable quality of life.

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