Outcome of patients with severe AL amyloidosis and biopsy-proven renal involvement ineligible for bone marrow transplantation

OUTCOME OF PATIENTS WITH SEVERE AL AMYLOIDOSIS AND BIOPSY-PROVEN RENAL INVOLVEMENT INELIGIBLE FOR BONE MARROW TRANSPLANTATION

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ABSTRACT

INTRODUCTION: AL amyloidosis is caused by a plasma cell clone. Due to the impact of the disease on patient survival, careful evaluation of organ involvement is essential. Treatment of AL amyloidosis should be adapted to the patient's degree of risk. AIM: We analyzed the clinical, laboratory and histological characteristics of 21 elderly patients (pts) (mean age 74.7 ± 7.97 yrs, range 55-81) with AL amyloidosis, including 17 patients (81%) with biopsy-proven renal involvement, who were ineligible for bone marrow transplantation, and evaluated the impact of renal impairment on survival. RESULTS: Cardiac and renal involvement was found in 67% of cases. Among the 17 patients with renal involvement, 12 had renal failure with proteinuria, and 1 showed isolated renal failure and vascular amyloid deposition. Hematological response was 57.1 % at first line therapy (75% after three cycles). With regard to renal outcome, 6 of the 17 patients with renal involvement responded: proteinuria decreased from 4.2 to 1.1 gr/24 h (range 0.2-3 gr/24 h) with stabilization or improvement of serum Creatinine (sCr) levels. Applying the Staging System for Renal Outcome in AL Amyloidosis to our pts with biopsy-proven renal amyloidosis proved to be unreliable. Only severe renal failure at diagnosis was found to directly influence patient survival. CONCLUSIONS: To our knowledge this is the only case series in which the whole cohort of patients with urinary or functional abnormalities underwent a histological evaluation. None of the patients were elegible for bone marrow transplantation. Hematologic response was 57.1%, while renal response was much lower (35%). Of note, the Staging System did not completely apply to this peculiar setting of patients in whom renal involvement was not presumptive but actually biopsy-proven. More aggressive approaches are needed in these patients to avoid the inexorable progression of the disease.

Key words: AL-amyloidosis, biopsy-proven kidney involvement, NT-proBNP, MGUS, FLC

INTRODUCTION

Systemic amyloidosis encompasses a group of diseases characterized by the production and deposition of misfolded proteins in the extracellular space of tissues and organs (1). The most frequent type is AL amyloidosis, characterized by the deposition of immunoglobulin light chains (2). The clinical manifestations of AL amyloidosis depend on organ involvement, but are rarely specific and mimic other more prevalent conditions. With the exception of the central nervous system, the toxic monoclonal light-chain proteins in AL amyloidosis can virtually damage all organs, most frequently the heart and kidney. Cardiac dysfunction commonly manifests as heart failure (3). Renal involvement usually presents with a nephrotic syndrome and progressive worsening of renal function (4).

Amyloidosis is difficult to diagnose because no single imaging, blood, or urine test is diagnostic, and histological examination of the affected organs is needed (5). Appropriate screening of patients with a clinical syndrome compatible with AL amyloidosis must include immunofixation of serum and urine, and immunoglobulin free light chain (FLC) detection. If immunofixation in the serum and urine is negative and the FLC (K:λ) ratio is normal, further evaluation is not usually carried out unless the clinical suspicion is strong (8,9). If the patient presents with clinical symptoms consistent with AL amyloidosis, and a light chain disorder is found, bone marrow biopsy is recommended. Biopsy of the iliac crest bone marrow combined with abdominal subcutaneous fat aspiration will identify amyloid deposits in 85-90% of pts (10). If both the fat and the bone marrow stain negative for amyloid, there is still a 10-15% chance that amyloidosis is present, and an involved organ should be biopsied if the degree of suspicion is high (11).

The presence of amyloid is unique proof of kidney involvement. Renal biopsy should be performed in all cases of urinary abnormalities despite positive staining in another tissue. The extent and distribution of renal amyloid deposition might also be important in order to carry out a comparison of the outcome of these patients (12).

Several reports have shown that patients with AL amyloidosis have a poor prognosis, and estimated mean survival ranges from 6 months to 3 years depending on the characteristics of the patient population (13,14). In recent series, 4-year overall survival rates ranged from 40% to 60%. However, in the presence of advanced cardiac damage approximately 30% of patients die within 1 year of diagnosis (1, 15). The use of widely available serum cardiac biomarkers, including serum troponin T and N-terminal pro–brain natriuretic peptide (NT-proBNP) allows us to stratify patients with a cardiac involvement. Using cut-off values of 0.035 mcg/L for troponin T and 332 pg/mL for NT-proBNP, patients can be classified into three stages. In stage I, both biomarkers are low (33% incidence). In stage III, both biomarkers are high (30% incidence). In stage II, only one of the two biomarkers is abnormal (37%). Reported mean survival times are 26.4, 10.5, and 3.5 months for stages I, II, and III respectively. The value of these cardiac biomarkers has been validated both in patients who underwent conventional treatment and in those treated with stem cell transplantation (SCT) (16).

Renal involvement is present at diagnosis in approximately 70% of pts with systemic AL amyloidosis who present with albuminuria (in the nephrotic range in about 40% of cases) (17,18). These pts are destined for end-stage renal disease (ESRD). The spectrum of renal morphological abnormalities is quite variable (19, 20). Proteinuria >5g/24 hrs and estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 predict progression to dialysis (6, 18, 21, 22). These cut-off values

served as a staging system to evaluate the risk of ESRD (23). Patients with eGFR above and proteinuria below the cut-off values (renal stage I) have a 0–3% risk of dialysis at 2 years. This risk increases to 11–25% in patients with either eGFR below or proteinuria above the cut-off values (renal stage II), and increases up to 60–75% in patients with both eGFR below and proteinuria above the cut-off levels (renal stage III) (Table I). Progression to ESRD has been shown to be a main determinant of morbidity in AL amyloidosis (24). This staging system was used in a large cohort of patients with a presumptive diagnosis (mostly based on clinical grounds) of kidney amyloidosis. Whether this staging system applies in patients with biopsy-proven renal involvement is presently speculative.

Elderly patients represent a subset of affected subjects made particularly frail by a number of co-morbidities (6). These patients are ineligible for bone marrow transplantation. They often undergo incomplete diagnostic procedures (especially renal biopsy), are treated less aggressively and receive lower doses of drugs as compared to younger pts (7). Thus, interpretation of the outcome of these patients is limited by the heterogeneous nature of the published series, both with regard to patient age and to definition of organ involvement (i.e., biopsy-proven vs clinical diagnosis) and the administered treatment. Hence, the clinical management of patients with AL amyloidosis who are elderly or ineligible for bone marrow transplantation remains a challenge.

Aim of the study

This study was especially aimed at analyzing the clinical, laboratory, and histological characteristics, and the outcome of patients with AL amyloidosis and biopsy-proven renal involvement who were not eligible for bone marrow transplantation. Whether the extent of renal damage impacts the patients' renal and life survival was also addressed. Timing of response to therapy was evaluated in order to improve the decision-making protocols.

Materials and Methods

One hundred and two of the 239 patients with amyloidosis recorded in the Registry of Rare Diseases of Piedmont and Aosta Valley (North-West Italy) between 2007 and 2018 were directly registered by our Center (Interregional Coordinating Center for Rare Diseases). Sixty-nine of them were receiving treatment in our Unit, including 52 systemic AL amyloidosis subjects, 31 of whom were ineligible for bone marrow transplantation and were taken into consideration for the present study. Ten were then excluded, including 5 who had been referred to other centers following diagnosis, 1 because of sudden death within one month of diagnosis, and 4 due to incomplete follow-up. Twelve males (57.1%) and 9 females (42.9%) were examined. Demographic data and causes for transplant ineligibility are summarized in Table II.

The end of the follow-up period was set for June 15, 2018, when new therapeutic strategies were introduced. All patients underwent bone marrow biopsy, and, starting in 2013, detection of the serum free light chains was carried out by nephelometry using Freelite Serum Free Light Chain Assays. Organ involvement was defined using the Consensus Criteria for Organ Involvement, as described elsewhere (24). Peripheral nervous system involvement was evaluated by electromyography and relief of orthostatic pressure. Cardiac involvement was assessed by echocardiography and by measuring serum levels of NT-proBNP. Renal function was assessed by measuring eGFR using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula and by detecting proteinuria obtained by 24-hour urine collection. Renal biopsy was systematically performed in pts presenting with at least one altered parameter. Histological diagnosis of

AL amyloidosis was confirmed by Red Congo staining. Renal response was defined as ~~a~~ proteinuria with a >50% reduction and/or normalization or improvement of renal function. The Staging System for Renal Outcome in AL amyloidosis was also evaluated (22). By definition, none of the patients were eligible for bone marrow transplantation. First line therapy was bortezomib-based, in combination with corticosteroids with or without cyclophosphamide or melphalan. Hematological response was assessed using the 2012 ISA criteria (23). Clinical response was defined as an improvement in organ function or performance status. All pts were evaluated at 3, 6, 12, 24 and 36 months after diagnosis by examining hematological response, biomarkers of involved organs, and clinical complications.

Clinical information was retrieved from medical records, and the clinical and demographic features were recorded with respect to age and other demographic information, clinical presentation, extent of histological renal damage, proteinuria and renal failure, and bone marrow biopsy.

Statistical analysis

Data were expressed as a percentage for categorical variables and as mean (interquartile range [IQR]) for continuous variables. Between-group comparisons were performed by Chi-squared or Fisher's exact tests for categorical variables and by Mann-Whitney test or Kruskal-Wallis with Dunn's post hoc test for continuous variables. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

Results

This retrospective study includes 21 cases of AL amyloidosis diagnosed at our Center between January, 2007 and March, 2018. This cohort of 21 pts, including 17 pts with biopsy-proven renal involvement, was followed-up for a mean of 33.7 ± 22.5 months (range: 5-90 months) after diagnosis. Mean age at diagnosis was 74.7 ± 7.97 yrs (range 55-81). Notably, 16 pts (76.2%) were >70 years old, including 7 pts (33.3%) who were ≥80 years of age. Mean follow-up after diagnosis was 33.71 ± 22.5 months (5-90 months). At the time of writing 10 pts were still alive. At diagnosis, 8 pts (38%) presented with hypertension, 3 pts (14.3%) with prior ischemic heart disease, 2 (9.5%) with non hematological neoplasms, 1 pt (4.8%) with chronic obstructive pulmonary disease (COPD), 1 pt with chronic renal failure, 1 pt with heart failure and 1 pt with diabetes mellitus.

Each pt underwent bone marrow biopsy. Amyloidosis was associated with a monoclonal gammopathy (MGUS) in 6 pts, with smoldering myeloma (SM) in 6 pts, with multiple myeloma (MM) in 6 pts, and with lymphoma in 1. No hematologic abnormalities could be detected in 2 pts.

Amyloid deposits were found in 9/21 bone marrow biopsies. Fourteen out of 21 pts (66.6%) had cardiac involvement, 11/21 (52.38%) had peripheral nervous system involvement and 3/21 (13.63%) had gastrointestinal involvement. Seventeen out of 21 pts (81%) had kidney involvement (with no detectable extrarenal signs in 4 of them). The number and type of involved organs are shown in Figure 1.

Data on serum free light chains (sFLC) were available for 16 pts. sFLC ratio was altered at the time of diagnosis in 11 of them.

Mean NT-proBNP was 3,303.35 ng/L (SE 939.51) with 10 pts having a concentration >1,800 (i.e., Mayo stage 3b disease) (6) (Figure 2). Hematological responders had significantly lower pro-BNP levels both at baseline and during follow-up (Figure 3). Ninety per cent of pts with values above 1,800 ng/L at diagnosis died during the follow up, while 90% of pts with values below 1,800 at baseline were alive at the end of follow up.

Twelve pts had renal function impairment (RFI) and proteinuria (in the nephrotic range in 9 out of 12 cases); 1 patient had isolated RFI (with prevalent vascular amyloid deposition at renal biopsy), and 4 pts had non-nephrotic proteinuria. Three out of 17 pts were undergoing hemodialysis at the time of diagnosis. Of the remaining 14, the mean sCr value at diagnosis was 1.51 ± 0.82 mg/dL (0.6 to 9.04 mg/dL); mean eGFR was 45.01 ± 16.2 ml/min (3-102 ml/min). The mean proteinuria value was 4.63 ± 2.4 g/24h (0.2 - 10 g/24h).

Extensive amyloid renal infiltration was found in all patients with decreased eGFR and or proteinuria. In one case, amyloid deposits were associated with extra-capillary proliferation. Nine out 17 pts had a diffuse pattern characterized by vascular, glomerular and interstitial amyloid deposition; 5 of 17 pts had vascular and glomerular amyloid deposition, 2 pts had glomerular and interstitial deposition and 1 pt had a vascular-limited pattern. A marked positivity (+++) for the substance P was observed in all the biopsies. In 7 cases amyloid was organized in spicules along the capillary wall.

Five pts underwent a repeat biopsy during follow-up to evaluate the response to therapy and quantify organ damage. In 3 cases increased amyloid deposition was found, 1 showed improvement (Figure 4) and 1 showed unchanged features.
At the time of the present analysis, 10 of the 17 pts with renal involvement had died and 7 were still alive (mean follow-up of 18.33 months and 47.38 months, respectively). The mean eGFR values at diagnosis were 20.6 ml/min and 59.1 ml/min, respectively.
Altogether, 12 of 21 patients (57.1%) had complete *hematological response* to therapy (10 after first line treatment, and 2 after the second therapeutic line). Among the 10 pts who responded to first line treatment, 8 achieved complete response after 3 cycles of therapy, while the remaining 2 did so after 6 cycles. Six of them were disease-free at their last follow-up (47.17 ± 17.20 months); 2 pts relapsed 30 months after diagnosis and 2 pts died during follow up, 15 and 19 months after diagnosis, respectively. The 24- and 36-months survival was 66.6% and 47.4%, respectively.
With regard to *renal response*, 6 out of 17 pts responded to therapy and achieved a 50% reduction in proteinuria when compared to baseline (from 4.2 gr/24 h, range 0.5-6.2 gr/24 h, to 1.1 gr/24 h, range 0.2-3 gr/24 h), ($p<.05$) with stabilization or improvement of sCr (from 1.35 mg/dl to 1 mg/dl), ($p<0.05$) and eGFR (from 61.2 ml/min to 70.3 ml/min).
We observed no differences between responders and non responders with regard to age, extent of renal impairment, or level of proteinuria. Our data showed that achieving renal response as defined above required complete hematological response. Six of the 9 responders (based on the hematological criteria) also had a renal response, while none of the 8 pts who did not show a hematological response had any improvement in proteinuria or renal impairment. All responders showed a halving of proteinuria during the first six months of therapy that persisted or further improved during the follow-up period (>24 months in 4 pts, 3 of whom had <0.5 g proteinuria at the last observation).

Patients with renal response had myeloma–associated amyloidosis in 2 cases, monoclonal gammopathy in 2 cases, lymphoma in 1 and "idiopathic" amyloidosis in the remaining patient. Four of these 6 pts were given a bortezomib/desametasone regimen (plus melphalan in 2 cases and cyclophosphamide in another case). The lymphoma patient was treated with Rituximab plus glucocorticoids. The remaining patient was treated with Cyclophosphamide, dexamethasone and lenalidomide.

We applied the current staging systems to our cohort. According to Palladini's renal staging (23), 4 (28.6%), 6 (42.8%) and 4 (28.6%) patients were in renal stages I, II and III, respectively. During the follow-up, none of the patients with a baseline proteinuria <5 g/24h and an e-GFR >50 ml/min per 1.73 m^2 (renal stage I) progressed to dialysis. However, we did not observe any difference in progression rate between stages II (33%) and III (25%). According to Kastritis's renal staging (18), 3 (21.4%), 4 (28.6%) and 7 (50%) patients were allocated to renal stage 1, stage 2 and stage 3, respectively. None of the patients with renal stages 1 or 2 required dialysis. Three patients (43%) with renal stage 3 began dialysis 2 years after diagnosis. The system was able to distinguish renal survival between renal stage 3 and renal stages 1 and 2.

Discussion

The prevalence of hematologic malignancies and other clonal blood disorders, including amyloidosis, increases with age.
The average age at diagnosis of the present cohort of AL amyloidosis was 74.7 ± 7.9 years, with 76.2% of patients older than 70, 33.3% of whom were ≥80 yrs. Studies addressing the progression and prognosis of AL amyloidosis in this population are lacking, and little is known about the potential for response to chemotherapy in such patients who are almost invariably ineligible for bone marrow transplantation.
Despite age, rate of complete hematological response (57%) and survival, data in this cohort were similar to series that included large proportions of less compromised patients (25-31). This is of particular interest when considering that the vast majority of our patients have unequivocal (biopsy-proven) renal involvement.
In our cohort, the rate of cardiac involvement was found to be high, and NT-proBNP levels were elevated in 100% of the patients, even in the absence of clinical symptoms, thus confirming the relevance of NT-proBNP in identifying high risk patients, in the early stages of the disease. Of interest, follow-up NT-proBNP levels at baseline were significantly lower in responders than in non-responders ($P<0.05$). NT-proBNP represents one of the main prognostic factor of the Mayo Risk Stratification System 2012 (16). Using the same cut off-of value, 90% of patients with NT-proBNP levels >1,800 ng/L at diagnosis died during follow-up, while 90% of patients with values <1,800 ng/L were still alive at the end of follow-up.
Involvement of the peripheral nervous system was detected more often than reported (i.e., 52.4 % vs 15%) (32). Notably, all patients at our Center systematically undergo nerve electromyography evaluation at the time of diagnosis regardless of the presence of symptoms. This approach should be extensively used considering that most patients are candidates for bortezomib-based regimens.
With regard to kidney involvement, the frequency of detectable proteinuria was higher than in other series (94% vs 70%) (32), as was the extent of proteinuria (75% with >3.0 g/day vs 60%), and the degree of renal impairment (stage 3A – CKD) (76% vs 50%). Amyloid deposits were detected in all patients who underwent renal biopsy at the time of diagnosis. These data are unique since renal biopsy is not routinely performed in these patients who are considered at greatest risk of

complications. This is a classic myth, related to the fact that pts with AL amyloidosis are often managed by non nephrologists.

Data regarding our cohort show that good hematologic response does not necessarily imply an actual organ improvement. Conversely, in the absence of complete hematological response no renal response can be expected. A subset of patients showed renal progression with normal monoclonal FLC levels (or with levels consonant with the extent of renal impairment). Recently, newer methods for evaluating hematologic response, such as flow cytometry and next generation gene sequencing, have enabled the detection of malignant clones that are undetectable by standard analyses (33). These methods might reveal the small amount of circulating amyloidogenic light chain that is responsible for the progression of renal disease in these cases. It has been suggested that further standard chemotherapy could obtain an improvement in organ response in these resistant cases (34).

Currently, determining proteinuria (0.5g/24h) and renal function still remain the standard criteria in the assessment of renal involvement (23). This approximation likely contaminated several patient cohorts and made outcome data of putative renal patients difficult to interpret. Proteinuria and/or renal impairment should not be considered *per se* sure biomarkers of renal involvement especially in elderly patients who have a number of possible independent co-morbidities. An elderly AL amyloidosis patient with proteinuria, especially in the sub-nephrotic range, should not be assumed *a priori* to be a patient with renal amyloidosis. The detection of amyloid deposits is unique proof of kidney involvement, and renal biopsy should be performed in all cases of urinary abnormalities despite positive staining in other tissues. Moreover, the extent and distribution of renal amyloid deposits can also be important when comparing the outcomes of these patients (33,35).

In the present study 5 patients underwent a second biopsy in order to evaluate response to therapy and degree of chronic damage. Among them, one did not show histological progression and one was found to improved. Amyloid deposition is hard to resolve. More effective treatments than those currently available are probably needed to reverse or limit renal deposition. These regimens should be used soon before irreversible damage occurs. The standard escalation of treatments while searching for optimal control of the hematological disorder should not be applied to cases characterized by rapid disease progression with renal involvement. In other words, the escalation approach, which is a milestone of hematologic treatment, may result in a definite delay of effective treatment and accumulation of irreversible lesions.

These patients should be treated aggressively *ab initio*.

Among the emerging non conventional agents, early studies have provided encouraging data regarding the safety and tolerability of the anti-CD38 monoclonal antibody in AL amyloidosis (36,37).

Conclusions

This is a retrospective study on patients affected by AL amyloidosis who were ineligible for bone marrow transplantation. Studies on such patient cohorts who are by definition excluded from clinical trials, are lacking. To our knowledge this is the only case series including a vast majority of pts with urinary or functional abnormalities who systematically underwent histological evaluation. That makes this contribution unique to the literature and sets the scene for future large-scale prospective studies to further investigate this type of patients.

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