

# Amyloidosis: is a cure possible?

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## introduction

The amyloidoses are protein misfolding diseases in which different soluble proteins aggregate as extracellular insoluble fibrils. This process causes organ dysfunction and death, unless it is arrested by therapy. So far, 25 types of amyloidosis have been classified according to the protein forming the amyloid deposits. In AL amyloidosis, a usually small-sized bone marrow plasma cell clone produces toxic light chains that cause multiple organ damage and fibrillar deposits [1]. Only a minority of monoclonal light chains form amyloid fibrils, probably due to specific mutations that destabilize the protein favoring its misfolding and aggregation. In the last few years, a better understanding of the pathogenesis of the disease, new markers of prognosis and response and innovative therapies have improved the care of patients with AL amyloidosis, with a profound impact on the natural history of the disease.

## clinical presentation and diagnosis

AL amyloidosis is the most common form of systemic amyloidosis in western countries with an approximate incidence of 10 patients per million person-year. During the course of multiple myeloma, 10–15% of patients develop overt AL amyloidosis. In 868 patients referred to the Pavia Amyloid Center, the median age was 62 years and there was a slight preponderance of males (57%). Seventy-two percent of patients had renal involvement, which usually presents with proteinuria (nephrotic syndrome in 53% of cases), 63% had cardiac amyloidosis, 26% had liver involvement and 19% and 16% had peripheral and autonomic nervous system involvement, respectively. Sixty-eight percent of patients had more than one organ involved at diagnosis. Cardiac amyloidosis manifests with heart failure and/or arrhythmias and is diagnosed based on elevated ventricular thickness at echocardiography, which is almost invariably associated with a high serum concentration of natriuretic peptide type-B (BNP) and its N-terminal propeptide (NT-proBNP). Hepatomegaly with elevated serum alkaline phosphatase is the hallmark of liver involvement. Amyloid peripheral neuropathy is predominantly sensitive, axonal, symmetrical and progressive. It is often associated with autonomic neuropathy, causing postural hypotension, gastrointestinal symptoms (constipation, diarrhea, anorexia and weight loss), and impotence. Highly suggestive findings

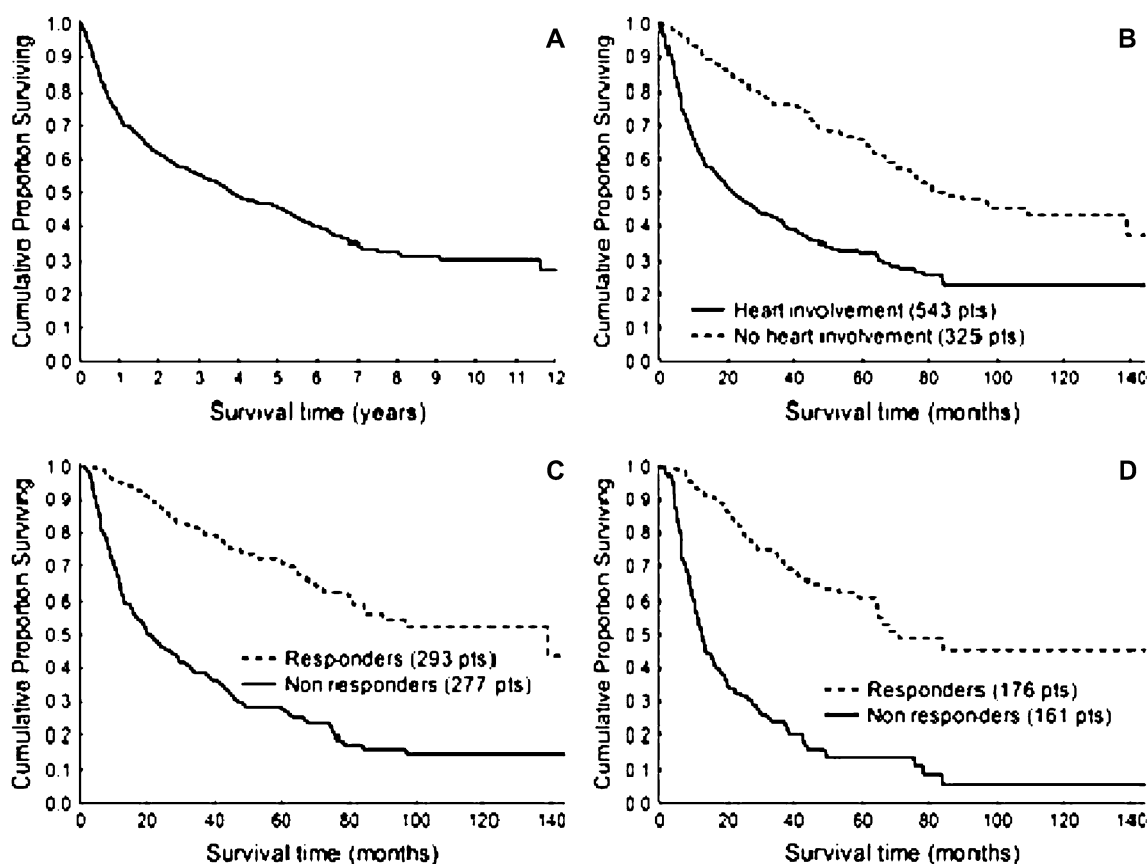
include macroglossia and periorbital purpura, which occur in ~15% of patients.

The diagnosis of amyloidosis requires the identification of amyloid deposits in tissues. The aspiration of abdominal subcutaneous fat can substitute biopsy of the organs involved in the majority of patients (sensitivity 88% in our patient population). The characterization of amyloidosis as AL type requires the demonstration of the underlying plasma cell clone. The number of bone marrow plasma cells is usually small (median 7%) and was within normal range in 34% of the patients evaluated at our center. However, a monoclonal plasma cell population can be detected in bone marrow aspirates by immunofluorescence in >80% of patients. Screening serum electrophoresis is inadequate, because it does not show a monoclonal spike in nearly 50% of cases. Thus, all patients should undergo good resolution immunofixation electrophoresis of both serum and urine, which could detect a monoclonal component (with  $\lambda/\kappa$  ratio of 75/25) in 97% of the 868 patients evaluated at our center. The measurement of circulating free light chain (FLC) is a useful diagnostic complement (sensitivity 76% in our patient population). The mere coexistence of systemic amyloidosis and a plasma cell clone is not conclusive evidence of AL amyloidosis. The chance association of a monoclonal gammopathy and of non-AL (reactive, hereditary or senile) amyloidosis has been reported by several groups. Since the treatment is radically different in the various types of systemic amyloidosis, amyloid typing is necessary and demands adequate techniques such as immunohistochemistry, immunoelectron microscopy, mass spectrometry-based methods and genetic testing, to identify the specific mutation in the hereditary forms [1].

## assessment of prognosis and response to therapy

The median survival of 868 patients with AL amyloidosis followed at our center was 3.8 years, with 27% of patients dying within 1 year from diagnosis and a 10-year cumulative proportion surviving of 31% (Figure 1a). Death was due to cardiac amyloidosis in 75% of the 393 patients who died (sudden death 25%). Cardiac involvement negatively influenced survival (Figure 1b), whereas hematologic response resulted in a significant advantage both in the overall population (Figure 1c) and in patients with cardiac amyloidosis (Figure 1d). Cox multivariate analysis showed that the only two significant independent prognostic determinants were cardiac

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**Figure 1.** (A) Overall survival of 868 patients with AL amyloidosis followed at the Pavia Center for Amyloidosis (median 3.8 years). (B) Survival according to heart involvement (median 21 versus 82 months,  $P < 0.001$ ). (C) Survival according to response to chemotherapy in 570 patients (median 21 versus 108 months,  $P < 0.001$ ). (D) Survival according to response to chemotherapy in 347 patients with heart involvement (median 12 versus 70 months,  $P < 0.001$ ).

involvement and hematologic response to therapy ( $P < 0.001$ ). The degree of cardiac dysfunction can be accurately defined by measuring serum NT-proBNP and this marker, in association with cardiac troponins, allows an accurate risk stratification [2].

The measurement of circulating FLC is necessary for monitoring response to therapy. A  $>50\%$  reduction of circulating FLC is associated with improved survival, but immunofixation-negative complete remission (CR) grants a survival advantage over partial response [3]. In patients with cardiac AL amyloidosis, the serum concentration of NT-proBNP drops rapidly if the reduction of circulating FLC is adequate, translating into prolonged survival. This allows tailoring of anti-clone therapy based on organ and hematologic response, improving the toxicity/benefit ratio and permitting prompt initiation of second-line therapy in refractory patients.

## therapy of AL amyloidosis

The aim of therapy is to rapidly reduce the supply of the amyloidogenic FLC in order to restore organ function and prolong survival. This is done by targeting the plasma cell clone producing the amyloidogenic light chain [1]. Most of the treatment strategies used in AL amyloidosis derive from multiple myeloma therapeutic regimens. However, patients with AL amyloidosis not only have a hematologic malignancy,

but also present with dysfunction of one or more organs, which renders them particularly susceptible to the toxic effects of chemotherapy. Since a considerable proportion of patients with AL amyloidosis present with advanced organ dysfunction, a rapid response is also imperative. Supportive care is fundamental and aimed at maintaining quality of life, delaying organ failure and prolonging survival while specific treatment has time to take effect [1]. Organ transplantation can be offered to patients who attain CR but have irreversible organ damage, but can also represent an option to render a patient with end-stage organ failure eligible to the high-dose chemotherapy [sequential solid organ and autologous stem cell transplantation (ASCT)]. More than 10 years ago, it was shown that patients with AL amyloidosis receiving melphalan plus prednisone (MP) survived longer than patients who were not exposed to chemotherapy [4]. However, the response rate to MP is  $\sim 30\%$  and one-third of patients require more than 1 year to respond. The introduction of ASCT represented a major breakthrough in the therapy of AL amyloidosis. When performed with high-dose melphalan (HDM,  $200 \text{ mg/m}^2$ ), ASCT grants a high hematologic response rate (76%, CR 33%), which is associated with improved survival and quality of life [5, 6]. However, treatment-related mortality (TRM) is high (10–12%), particularly in patients with heart failure and multiorgan involvement. With the aim of reducing TRM, a risk-adapted modulation of the dose of melphalan

(140–100 mg/m<sup>2</sup>) has been proposed. However, dose reduction translated into reduced hematologic response rate (53%) with a still considerable TRM (16%) [6]. High-dose dexamethasone was tested in AL amyloidosis in a multicenter trial, observing a 53% hematologic response rate (CR 24%) and organ response in 45% of cases [7]. Median time to response was 3.4 months. The high dose schedule of dexamethasone (40 mg on days 1–4, 9–12, 17–20 every 35 days), used during induction therapy, was associated with substantial toxicity (TRM 7%). In 1999 we started a trial of oral melphalan plus dexamethasone (MDex) in patients ineligible for ASCT [8]. Despite the fact that we treated patients with advanced disease, we observed a high hematologic (67%, CR 33%) and organ (48%) response rate. Four percent of subjects died during treatment and 11% experienced severe adverse events. Median time to response was 4.5 months. Responses to MDex resulted in a significant survival benefit and were durable, with complete remissions being maintained for >3 years in 70% of cases. Median survival was 5.1 years. More recently, a French multicenter randomized trial failed to demonstrate a response and survival advantage for ASCT compared with MDex [9]. The transplant-related mortality in this multicenter study was high (24%) and a quarter of transplanted patients received a reduced dose of melphalan (140 mg/m<sup>2</sup>). It has been argued that this may have influenced the results. However, a landmark analysis of survival excluding early deaths showed no differences between MDex and ASCT. Thalidomide was tested in association with dexamethasone (TDex) as second-line treatment and induced a clonal response in 48% of patients (CR 19%). Median time to response was 3.6 months and severe adverse events were frequent (65%), but no TRM was reported [10]. After ASCT, TDex improves the rate and extent of response [11]. A risk-adapted association of cyclophosphamide, thalidomide and dexamethasone (CTD) has been evaluated in patients with AL amyloidosis [12]. The hematologic response rate was high (74%) and response was obtained after the first cycle in 50% of patients. The monoclonal component disappeared at immunofixation in 15% of cases and the organ response rate was 27%. Four percent of patients died during treatment and 32% experienced severe adverse events. Treatment with CTD has the advantage of allowing subsequent stem cell mobilization, but data on the duration of response have not been published yet.

The potent thalidomide analog lenalidomide has been studied in AL amyloidosis in two independent clinical trials. In the study by the Mayo Clinic group, the hematologic response rate to lenalidomide alone was 4%, but when dexamethasone was added it rose to 45% [13]. Overall, the organ response rate was 23%. Eighteen percent of patients died during treatment and severe adverse events were observed in 86% of cases. In the trial by the Boston Group, the hematologic response rate to lenalidomide alone was higher (21%), but the addition of dexamethasone still improved the results, obtaining an overall 53% hematologic response rate (CR 21%) [14]. The organ response rate was 21%. A phase II clinical trial of cyclophosphamide, lenalidomide and dexamethasone is under way at our center.

The proteasome inhibitor bortezomib is being tested in a phase I/II multicenter trial and the preliminary results show that a once-weekly schedule of 1.6 mg/m<sup>2</sup> every 35 days was

well tolerated. Overall hematologic response rate was 47% (CR 21%) and 40% of patients experienced severe adverse events. Kastritis et al. [15] reported a high hematologic response rate (83%, CR 39%) and a very short time to response (0.9 months) to bortezomib associated with dexamethasone, indicating that this regimen may be exploited in future trials in patients with rapidly progressing disease.

## conclusion

Thanks to the availability of biomarkers of hematologic (FLC) and organ (BNP and troponins) response and of new treatments, we now have the means to approach optimal management of AL amyloidosis. Chemotherapy should be guided by frequent measurement of FLC and organ function in order to assess cycle by cycle the toxicity/benefit ratio. At present, one-third of patients is projected to survive longer than 10 years and this figure is likely to improve with the introduction of new drugs. The follow-up of these long-term surviving patients will show whether a cure is possible.

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