Primary amyloidosis (AL): treatment and prognosis

Margarida Ascensão*, Helena Figueiredo**, Mª José Nabais**, Paula Pimenta**, Francisco Parente**, Ana Paiva***, José Feio****, Borges Alexandrino*****, Políbio Serra e Silva******

Abstract

Primary amyloidosis (AL) is an entity with a bad prognosis, where the various therapeutic measures have little influence.

The authors present 7 patients with this diagnosis, who underwent AL treatment regimes.

The authors comment on the patient's survival, prognosis signs and the syndromes present at the time of diagnosis, as well as the symptomatic and functional evolution with the different treatment regimes and the side effects they presented.

Key words: Primary systemic amyloidosis, AL, treatment, prognosis, alpha-interferon, chemotherapy.

Introduction

Primary systemic amyloidosis (AL) is a rare disease, corresponding to an immunocyte dyscrasia.[1,2] It is characterized by the production of intact monoclonal light chains and/or their fragments, which may be deposited as amyloid in the tissues and/or organs, leading to a change in their structure, and ultimately, death.[3,4,5]

It was found that light chains in the urine of patients with AL amyloidosis, when purified and injected into rats, reproduced the disease. The "amyloidogenicity" inherent to certain monoclonal light chains was then confirmed in vivo, although the pathophysiological mechanisms remain unclear.[2,6,7]

This disease has very poor prognosis because it is usually incurable and progressive, and there is no effective therapy.[2,8,9,10,11] The mean survival after diagnosis varies according to the case series and ranges from under 12[9,12,11,13,14] to 20 months.[1,11,15,16] The trend to longer survival rates observed in recent years[15] may be due to the greater number of diagnoses in earlier stages of the disease through the use of less invasive and equally sensitive techniques (e.g., abdominal wall fat pad test for amyloid, echocardiography)[17] and the increased knowledge and capacity of clinical suspicion.

It has been observed that the prognosis is also dependent on the clinical syndromes observed at the time of diagnosis. This fact led some authors (Kyle et al.) to study the possible prognostic factors[9,12] (*Table 1*), enabling the classification of patients according to risk (high, moderate or low).[12] For example, it was found that cases with worse progression were those that manifested heart insufficiency, in which survival was four to eight months.[1,9,13,15] Patients with initial manifestations of peripheral polyneuropathy, with or without carpal tunnel syndrome, showed longer survival, both before diagnosis (symptoms beginning two years before), or after diagnosis, with survival times of between 30 and 50 months.[1,9,13,15,18] In some published cases, a tendency towards longer survival in females (25 months for women and 17 months for men)[1] was also observed.

The classification of patients by risk is important for further evaluating the influence of the therapy, enabling a comparison between groups.[12,15]

Most patients die from heart failure (40%) or uremia (6%), although liver insufficiency, gastrointestinal bleeding, sepsis and respiratory insufficiency may also lead to death.[2,10,11,13]

For the development of better treatment methods, more knowledge is needed of the factors responsible for the conversion of a soluble precursor into insoluble aggregate, which is deposited and compromises tissue function. The main objectives are prevention of amyloid precursor synthesis, preventing the de-

*Resident to the Internal Medicine Supplementary Internship

**Internal Medicine Hospital Assistant

***Resident to the Supplementary Internship in Nephrology

****Hospital Pharmacist

*****Graduate Assistant in Internal Medicine

******Head of Service

Medicine Service II of the Universidade de Coimbra

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TABLE I

Prognosis factors of AL amyloidosis

Factors that indicate a poor prognosis at the time of diagnosis	
In the first year (Kyle et al.)[12]	Congestive heart failure Monoclonal light chains in the urine Hepatomegaly Multiple myeloma
In the subsequent years (Kyle et al.)[12]	Creatinaemia Multiple myeloma Orthostatic hypotension Serum monoclonal protein
Others (Gertz & Kyle)[12,15]	Male Increased b2M Howell-Jolly bodies in peripheral blood Plasmacytosis Isolated peripheral polyneuropathy Monoclonal protein (in the first year only)
Factors indicating a good response to therapy	
(Fielder et al.)[41]	Absence of amyloidotic cardiopathy Presence of light k chains

posit of amyloid fibrils in the tissues and, ultimately, the promotion of fibril dissolution and removal of tissues.[9,19,20]

Various therapy regimens have emerged (*Table 2*). The most frequently used are the combination of melphalan/prednisone (MP) and colchicine.[9]

Although benefits have been reported for all of these regimens, such as clinical or laboratory improvement of certain syndromes[1] and even, in some cases, longer survival for some subgroups of patients,[2,16] no satisfactory therapeutic regimen has been developed. Nevertheless, the existing treatments are acceptable, given the poor prognosis associated with this disease.

Assessment of the response to the therapy is not easy either: a histological confirmation is not always possible and may be associated with false negatives, also, it may not allow the quantification of the amyloid; on the other hand, clinical or laboratory remission may not match the regression of tissue deposits and, therefore, of the disease.[9,14,21,22,23,24]

Thus, there is a need for the use of new therapeutic agents and other strategies.

Recently, advances in information on the natural history of amyloidosis have been made through the development of new techniques, such as ^{123}Tc-labelled

TABLE II

Therapy regimens

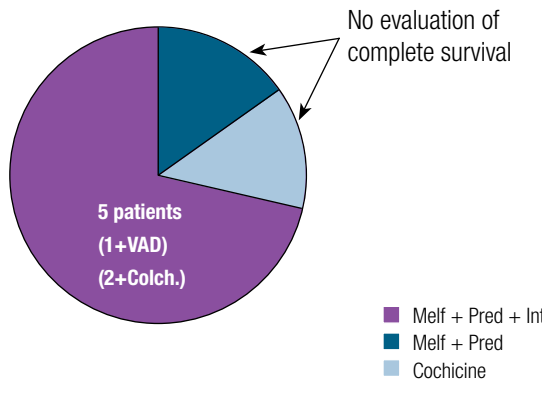
Melphalan + Prednisolone
Colchicine Melphalan + Prednisolone + Colchicine
Other cytostatic drugs (VAD)
DMSO, vitamin E, vitamin C, ...
α-interferon

SAP.[25,26] Through this technique, monitoring the therapy by measuring the amyloid substance body "load" and its variation in time is possible.[27,28] This method, which unfortunately is not yet available here in Portugal, revealed what some authors have already reported, though without credible evidence, concerning the possibility of regression of the tissue deposits. It has been demonstrated that these deposits are not inert and can be mobilized from the tissues, which in some ways, revolutionized the concept of amyloidosis, resulting in promising hopes.[26,28,29]

Material and methods

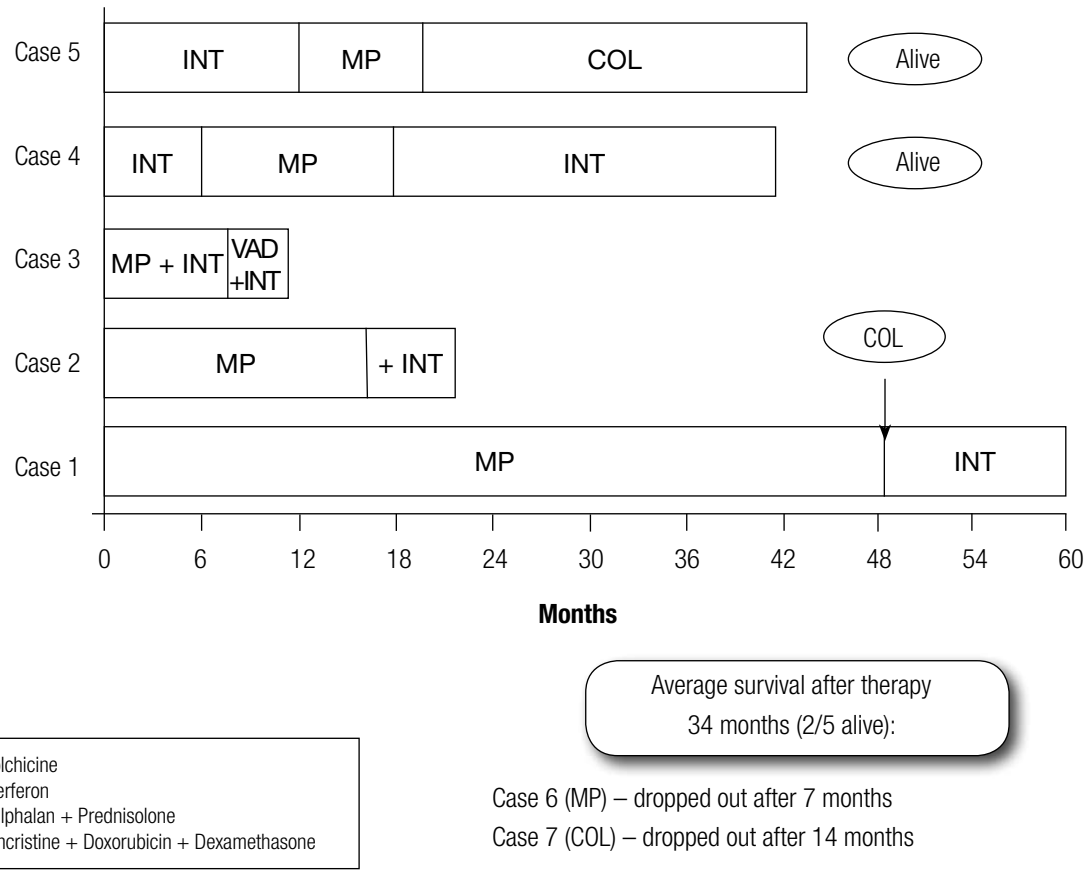
Based on an earlier study conducted at the Medicine II, involving our cases with unfamiliar systemic amyloidosis, we selected all patients with AL amyloidosis and without multiple myeloma, who received any treatment regimen between 1985 and 1994.

The objective of this study was to perform a retrospective investigation of the survival of these



Amyloidosis AL - therapeutic regimens.

FIG. 1



Amyloidosis AL - Therapeutic regimens and survival.

FIG. 2

patients, linking it to the indices of prognosis by Kyle et al.[12] and to the syndromes present at the start of the therapy, the analysis of symptomatic and functional evolution with the treatment, and the respective side effects.

Results

Seven patients diagnosed with AL amyloidosis were selected, three males and four females. The average age was 71.4 years.

The treatment regimens administered were (*Fig. 1*): melphalan combined with prednisolone (MP) to six patients, colchicine to three patients, vincristine combined with doxorubicin and dexamethasone (VAD) to one patient, and interferon to five patients. The complete survival of two patients is unknown, since they left the study at seven and fourteen months. With regard to the remaining five patients, three died and two are alive; the mean survival after therapy is 34 months (*Fig. 2*). The causes of death were heart failure in one and uraemia in two of the patients.

Five patients showed clinical or laboratory improvement after the therapy (*Table 3*).

Table 4 shows the various side effects experienced by these four patients. In two cases, the appearance of intense asthenia forced the discontinuation of the therapy with interferon (cases 4 and 5) and the start of treatment with MP (*Fig. 2*).

Colchicine, prescribed to only one of the patients (Case 1), caused severe digestive intolerance which led to its discontinuation.

Leukopenia occurred in three cases with the therapy with MP, requiring discontinuation in two of the cases. This association was also responsible for

TABLE III

Improvement after therapy

Case 1	MP	Extinction of light chains
Case 2	MP	Anemia, neurological symptoms
Case 3	MP + INT + VAD	Changes in coagulation (X Factor), purpura, edemas, ecchymosis, and swallowing.
Case 5	INT	Arthralgia, paresthesia
Case 7	COL	Arthralgia, sedimentation rate, anemia, hepatic tests

COL - colchicine; MP - melphalan + prednisolone; INT - interferon; VAD – Vincristine + Doxorubicin + Dexamethasone

TABLE IV

Secondary effects

Case 1	MP	Leukopenia → discontinuation
	COL	Digestive intolerance → discontinuation
Case 2	MP	Leukopenia (5 months)
Case 4	INT	Asthenia → discontinuation
	MP	Epigastralgia → discontinuation
Case 5	INT	Asthenia, prostration → discontinuation
	MP	Leukopenia

COL - colchicine; MP - melphalan + prednisolone; INT - interferon; VAD - Vincristine + Doxorubicin + Dexamethasone

the onset of upper abdominal pain in one patient, probably due to gastro-oesophageal reflux or candidiasis, secondary to prednisolone, leading to its discontinuation (case 4).

Table 5 shows the five patients who were used for the analysis of survival time, which was associated with the clinical syndromes and risk factors (according to Kyle et al.)[12] present at the time of diagnosis.

Discussion and conclusions

In our small sample, the average age was slightly higher (71.4 years) than that in other studies (approximately 62-64 years),[12,30] in which a prevalence of males (57%-65%) was also observed.[12,18] The therapy regimen most frequently used was the MP association (in six of the seven patients).

Alkylating agents, known to be partially effective in the process of proliferation of plasma cells (multiple myeloma), have been widely used in AL amyloidosis. Their aim is to suppress the abnormal clone of plasma cells responsible for the production of monoclonal light chains or their fragments, thereby also suppressing the precursor of amyloid fibrils deposited in the tissues. The MP combination has been used with some benefits, and several cases of resolution and/or regression of the amyloidosis after the start of the therapy have been reported (proven by I^{123}-labelled SAP).[3,11,26,30] It should be noted that in most cases, prolonged treatment (up to a year) may be required until a response is observed, and the treatment should not be abandoned too soon.[9,15]

Despite the risks (leukemia and myelodysplastic syndromes are frequent), particularly in prolonged treatment, it is believed that this combination, or the use of other cytostatic agents, are suitable as the first step in the management of the patients with a short life expectancy.[9,14,16,31,32,33]

In one of our patients (case 3), therapy with VAD was also used following the MP combination, due to clinical worsening after about five months of treatment with MP. For this patient, a favorable clinical and laboratory response was observed after the first and second rounds of therapy, with worsening after two months. The patient ended up dying.

This regimen has been used successfully for myeloma, which has led some authors to use it also in cases of primary amyloidosis, particularly after failure of alkylating agents, with reference to benefits.[34]

Also for this patient (case 3) alpha-interferon was administered at early stages, given its benefits in the treatment of multiple myeloma and the possibility of interference in the pathogenesis of AL amyloidosis.[24] This decision was made because of the poor prognosis, since cardiac involvement occurred, therefore, the patient belonged to the high risk group (survival of approximately four months), according to Kyle et al.

Its use has been proposed by various authors,[9,35] but to date, no benefit to the patient or objective regression of the disease has been observed, nor any prolongation of the patient's survival time, so it is now considered as a therapy that is not valid in this situation, and one that should be avoided.[4,9]

A likely contribution was found of these agents to the improvement of symptoms of patients 3 and 5, as well as to the prolongation of survival of patient 5 (*Table 3*). For patient 4, the use of these agents did not bring any benefits, so after about six months, it

TABLE V

Survival after start of therapy: syndromes and risk factors

	Survival time (months)	Clinical	Other pathologies	Risk factors
Case 1	60 F	Polyneuropathy		CL U
		Renal failure		PM S
		Proteinuria		
		Myocardiopathy		I R
		Orthostatic hypotension		OH
Case 2	22 F	Polyneuropathy		CL U
		Lymphadenopathy		
		Myocardiopathy		
Case 3	12 F	Myocardiopathy (CHF)		CHF
		Macroglossia, purpura		CL U
		Renal insufficiency		OH
		Carpal tunnel S.		
		Orthostatic hypotension		
Case 4	18 V	Paresthesia	Diabetes	CL U
		Myocardiopathy	Hyperthyroidism	PM S
Case 5	20 V	Carpal tunnel S.	PMR	PM S
		Macroglossia		
		Myocardiopathy		

was replaced with MP. Patient 1, also belonging to the high risk group due to cardiac and renal involvement, had hypotension and presence of light chains in urine (Table 5), and for patient 2, alpha-interferon was introduced as a last resort after intolerance to colchicine/MP, with no benefits.

Colchicine, which is also widely used for AL amyloidosis, particularly due to the remarkable benefits seen in other types of amyloidosis, such as familial Mediterranean fever,[2] is associated, in some studies, with an improvement in survival time;[15,30,36] and greater benefit has been obtained, with less organ involvement, in female patients.[9] Treatment should be continued and prolonged. Usually, adverse effects are not reported, except for gastric effects, which are rare.[2] Some authors suggest colchicine as an adjunct to the therapy with MP, reporting the possibility of synergism between the two regimens.[9] This agent was used in case 7, with significant clinical and laboratory improvement; however, this patient's survival time is unknown because the patient left the study. In Case 1, gastric intolerance prevented the use of this agent.

Other therapeutic strategies have been tested, such as dimethyl sulfoxide (DMSO), d-penicillamine, vitamin C, and among others (*Table 2*); however, no satisfactory benefits were observed, therefore it is less frequently used.[3,15,35,37,38]

We can conclude, therefore, that overall, benefits were seen with the above-mentioned therapies for most of our patients. However, the survival time remains short, with progressive evolution of the disease to death, so it is imperative to develop more effective therapeutic alternatives.

In view of this information, for the improvement of the patient's quality of life and survival, conservative and supporting measures are fundamental, and should be focused on the institutions involved; certain medical therapies may be necessary, and eventually

surgery.[15,18] Organ failure should be treated with drastic measures, and may include transplantation.

Although this is a systemic disease involving various organs and tissues, the prognosis has improved dramatically with the transplantation of organs, particularly heart and kidneys.[2,39] The medical treatment of various syndromes should be early and cautious.

For heart insufficiency, diuretics are advised, to reduce edemas. However, diuretics should be administered with caution, since these cases are at increased risk of hypotension, due to the possibility of hypoalbuminaemia, low ejection fraction or autonomic compromise.[15] Digoxin and calcium channel blockers are not indicated because they can decrease diastolic filling, aggravating heart insufficiency. In addition, these drugs are associated with a higher risk of toxicity in these patients, as they seem to bind selectively to the amyloid fibrils, increasing their concentration in the affected tissues. The effectiveness of ACE inhibitors is still not proven in these cases. Haemodialysis, although generally poorly tolerated, visibly improved the survival time of patients with renal involvement, which still was, nevertheless, shorter than that observed in patients undergoing haemodialysis due to other causes.[9,15] In these patients, death occurs as a result of cardiac involvement.[1]

We conclude that given the poor prognosis, practitioners should be aware of the possibility of this disease, so that they can identify it as early as possible, and initiate early therapy. We must not forget that in the absence of an effective treatment, it is necessary, first and foremost, to not harm the patient, and to avoid strategies that could be disastrous.[9,40] Nevertheless, we also should not forget that in our experience, AL had a shorter survival time than that of patients with multiple myeloma, which is subject to therapeutic measures. ■

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