Primary Amyloidosis: A Therapeutic Perspective

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Abstract

The authors emphasize the difficulties in the treatment of primary amyloidosis concerning not only the results but also the problems in evaluating its efficacy. Several therapeutics are reviewed and some considerations are made about the implication of treatment in the disease of the organs involved. Finally, they propose the alpha-interferon for treatment of primary amyloidosis.

Key words: primary amyloidosis, therapeutic, alpha-interferon.

Introduction

Primary amyloidosis (AL) has a very poor prognosis if no efficient therapies are used.[2] The survival of patients after diagnosis is approximately twelve months,[2] depending on certain factors. The worst prognoses are associated with heart failure, in which survival varies between four and seven months; while at the other extreme are cases which present peripheral polyneuropathy or carpal tunnel syndrome, with average survival ranging from thirty to fifty months.[3,4,5]

Although no satisfactory therapies have been discovered to date,[6,7] several regimens have been experimented in these patients. The most commonly used of these are the association of melphalan/prednisone and colchicine. Other therapies also worth mentioning are dimethyl sulfoxide (DMSO), vitamin E, and some cytostatics, such as cyclophosphamide, and the association of vincristine, adriamycin, and dexamethasone (VAD)[1,2,4,7,8] (*Table 1*).

All these regimens have been used in an attempt to find an efficient therapy for this condition, these experiments being justified by the poor prognosis of the disease. Most of these regimens have been used previously, with positive results in the treatment of other types of amyloidosis or conditions that are pathogenically related to AL amyloidosis, such as multiple myeloma. Theoretically, all the treatment hypotheses are based on the possibility of interrupting some of the stages of the amyloidosis chain, by suppressing the production of the amyloid precursor protein to prevent extracellular fibril deposits, or promote the disintegration and removal of this tissue deposits.[7,9]

Evaluating patients' response to therapy has been a difficult task. The histological follow-up has not proven reliable, not only because of the redistribution of the amyloid substance from one organ to another, but also due to technical difficulties – sometimes very small fragments are collected and mistakenly suggest amyloid regression and positive response to therapy.[9,10] However, sensitivity to therapy seems to vary from organ to organ. For instance, heart disease and macroglossia have proven to be more resistant than hepatic and renal impairment.[10,11,12] Given the impossibility of measuring the amount of amyloid, follow-up can only be done by assessing the organs involved, measuring the evolution of the monoclonal peak, and analyzing the quantity of monoclonal light chains in the serum and urine.[10,13] Nonetheless, these methods are not reliable, as there may be symptomatic regression with deposit intensification in the respective organs.[2,12,14]

Also, the reduction of light chains, or their fragments, does not necessarily lead to the regression of pre-established deposits.[15,16] This scenario can alter significantly with the emergence of methods that enable the extent of the disease to be established, such as scintigraphy, which uses iodine-123 to mark the amyloid P component.[17]

Despite these limitations, benefits have been found in the results of virtually every treatment, not only in isolated cases,[12,9,11,18] but also in some groups of patients, with alkylating agent therapy showing the best results.[13] However, when the analysis included all patients, no advantages were seen in terms of survival.[14,8] Due to the consistently poor results of

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the "etiological" therapies, conservative, supportive measures persist, playing an important role in the management of these patients, [19] while research on efficient treatments for this disease is carried out. [20]

Below, some regimens used to manage primary amyloidosis (AL) are discussed separately.

Melphalan + prednisone

This has been the most commonly used regimen for the treatment of primary amyloidosis, due to the results obtained in the treating of multiple myeloma. [21] Primary amyloidosis (AL) has a strong connection with this disease, and both are considered as belonging to the same condition. The distinction between AL amyloidosis and myeloma related to amyloidosis is considered artificial. [4, 18]

Primary amyloidosis develops when clonal plasma cells, albeit lacking the proliferating characteristic of myelomas, produce monoclonal light chains or fragments that have amyloidogenic properties, clustering to form a fibrillar structure and becoming deposited in organs, causing impairment of these organs.[17,22,23] Alkylating agents have been used with the aim of interrupting sequence, i.e., to eliminate or reduce the population of plasma cells responsible for the production of the amyloid precursor protein and, consequently, delay these deposits in the tissues. [1,2,7,12,22,24] Another proposed method is based on the hypothesis that amyloidogenic components develop after the abnormal production of immunoglobulins, which is reflected by the dominance of light chain fragments in relation to intact light chains – a condition that normalizes after cytostatic therapy. [25] With the lack of production and accumulation of the amyloid precursor protein, there is the possibility of dissolution or reabsorption of the existing deposits. [24]

The regimens adopted, despite slight variations, are based on studies on multiple myeloma that show a preference for therapy administered in four-day cycles with intervals of four to six weeks, and concomitant use of prednisone [26]. Some authors add to this association colchicine, [11, 20, 27, 28] other cytostatic drugs, [24, 29] or D-penicillamine. [9,30]

The inclusion of prednisone is due to the better response seen in cases of multiple myeloma, and an additional benefit of prednisone is that it is thought to decrease the production of immunoglobulins and increase their catabolism. [12,31] Nevertheless, other authors have raised the hypothesis that this influence may be harmful in that the alterations in immunoglobulin production and catabolism could lead to a higher production of light chain fragments with amyloidogenic characteristics. This hypothesis was developed by authors who used corticosteroid therapy in different regimens from that referred to above. [32,33,34]

TABLE I

Therapy for primary amyloidosis (AL)

- Melphalan + prednisone
- Colchicine
- Melphalan + prednisone + colchicine
- Other cytostaticS (VAD high doses of melphalan)
- Other less prominent options (DMSO D-penicillamine vitamin E)

*Management of impaired organs

* Proposed therapy >>>> alpha-interferon

The results achieved with this type of therapy have proven unsatisfactory and relatively imprecise, although some individual successful results can be highlighted.[7,18]

The studies of Kyle et al. are the ones with the highest number of patients.[6,13] A double-blind trial compared the use of melphalan/prednisone and that of placebo in a group of 55 individuals. No statistically significant differences were found in the survival of both groups. Benefits were found, however, in some patients of the melphalan/prednisone group, in particular, the disappearance of nephrotic syndrome in two individuals, the reduction of approximately 50% of proteinuria in eight patients, and a subjective improvement in one patient suffering from cardiac insufficiency. One meaningful feature of this study is that better results were achieved after patients were treated with melphalan/prednisone for a period of over one year.[6] A subsequent study, to compare the use of melphalan/prednisone with colchicine, showed that the former is the better regimen. [13] Despite the higher survival in the melphalan/prednisone group during this study, the findings have yet to be confirmed. The intercalating data of a randomized study, carried out by the same authors, suggests a higher survival with the melphalan/prednisone/colchicine regimen (18 months), compared to the melphalan/prednisone association (16 months), and colchicine alone (9 months).[20]

The literature includes several references to clinical cases in which benefits have been achieved with this regimen. Since most individuals in the group suffered from nephrotic syndrome, chemotherapy lead to a reduction of proteinuria and a consequent symptomatic regression.[9,10,12,14,15,24,27,35,36] Together with the reduction in nephrotic proteinuria achieved in some of these cases, an improvement was also observed in other conditions, namely myopathy,[36] altered digestive motility, skin lesions,[24] splenomegaly,[12] and improvements in hepatic impairment.[9,12,14,27] An important aspect, in some cases, was the control and even progression of other conditions, such as macroglossia.[12] Also, we would like to emphasize that several of these cases were patients with associated criteria of multiple myeloma or, at least, bone marrow plasmocytosis above 10%,[9,10,24,36] which might indicate a better response in the cases in which there is proliferation of the clonal plasma cells that produce the amyloid precursor protein. This fact is understandable if we take into account the activity of the alkylating agents.

In the absence of nephrotic syndrome, the references to improvements achieved with this therapy are more sporadic. One such case was an individual who suffered from hepatic amyloidosis and presented negative histological control after therapy, achieving survival of four years after diagnosis.[7] Schattner reports another case with hepatic impairment and additional bone lesion in which the patient not only achieved an improvement in clinical and laboratory indices, but also survived for four years. [11] Another manifestation of the disease that has achieved positive results is deficit in blood coagulation factors, namely factor X, with recovery of its levels and the disappearance of hemorrhagic disorders. [37] Despite the poor prognosis mentioned above, the literature, surprisingly, presents some cases of long survival. [18, 38] In one of these cases, a patient's disease reached 19 years of evolution, with tongue and heart involvement for seventeen years.[18]

The conclusion that there was a positive response to the melphalan/prednisone regimen in the cases referred is subject to criticism, due to the aforementioned limitations of the evaluation methods. Since histological control was negative in some cases, it was not carried out in the organs which showed clinical response.[11] In certain patients, although some of the biopsies did not detect amyloid substance, it was present in other organs submitted to biopsy,[2,24] and in others, authors have referred only to a reduction in tissue deposits, not their increase.[30,37] Sparking this debate on the inaccuracy of results, references can be found where, despite the reduction of nephrotic syndrome, authors have documented an increase in amyloid deposits in the kidneys.[14] Moreover, other authors have referred to spontaneous regression, i.e., in the absence of "etiological" therapies, but with subsequent progression to kidney failure.[39]

Considering the quite unsatisfactory results achieved through this therapy regime, to be trialled, its possible toxicity, particularly with regard to the risk of inducing leukemia, should be taken into account.

A recent publication of note on this subject is that of Gertz and Kyle. The authors mention that although 10 out of the 153 patients evaluated had cytogenetic alterations in the bone marrow, only four developed acute leukemia, and none of these cases emerged before the three years of melphalan therapy. In the patients who survived more than three and a half years, the risk was 21%. Therefore, this risk is only an actual threat to individuals whose survival goes beyond the aforementioned average time for this disease.[22,40]

As a final comment about this regimen, which is by far the most common for the treatment of this condition, we emphasize the recommendation to carry out a therapy test, as mentioned by several authors, despite the results achieved.[2,11,18,22,27,36,37] This recommendation is based on cases where a favorable response to therapy was obtained, and the poor prognosis in its absence. However, before introducing this association to an amyloidosis patient, one should, first of all, confirm the primary origin of the disease (AL), since no benefits have been proven in the treatment other types of amyloidosis.[2] The efficacy of this regimen is probably higher when administration begins prior to the existence of severe conditions, as this medication might reduce the amyloid deposits, but does not interfere in pre-established lesions; hence the interest in early diagnosis and therapy.[29,36] On the other hand, this association should be applied for six to twelve months before any lack of response can be considered. This is because although the treatment might suspend the production of amyloid substance, the dissolution of the deposits and consequent improvement of the pre-established lesions take some time.[12,24] Once improvement is achieved, interrupting

the therapy is another aspect to be considered, in view of the high frequency of leukemia and myelodysplasia cases in patients who have taken melphalan for over three years.[22]

Other cytostatics

Although less frequent than the association described above, several cytostatics have been used to treat primary amyloidosis (AL). Their use is based on the same motives that support the adoption of the melphalan/prednisone regimen described above.

Some authors have used cytostatics simultaneously or in sequence with the aforesaid association. This is the case, for instance, of cyclophosphamide[24] and vincristine,[29] whose benefits have been reported. In addition, Fielder reported seven cases that achieved response through different chemotherapy regimens, using adriamycin and bleomycin, among others.[10] There is also reference to response after therapy with high doses of alkylants, associated with autologous bone marrow transplantation.[41]

VAD is another association to be considered, that has achieved benefits in four primary amyloidosis patients,[1] due to its favorable effects on multiple myeloma.[42] It was initially used in cases which were refractory to alkylants,[42] then its introduction was proposed as the best treatment for multiple myeloma, [43] which can be eventually transposed to primary amyloidosis. Nonetheless, one should consider the risks of cardiotoxicity of anthracyclines and neurotoxicity of vinca alkaloids, which might limit the use of this regimen in amyloidosis patients with impairment of the related organs.[1,32] These regimens might be a valid alternative to the melphalan/prednisone association, and the literature presents cases of patients who used this regimen unsuccessfully, but achieved benefits with other cytostatics, such as VAD [1] and ALP (adriamycin, belustine, prednisone).[44]

Colchicine

The use of colchicine to treat this disease is based on its proven efficacy against another type of amyloidosis; that observed in patients suffering from familial Mediterranean fever (FMF).[45,46] It was initially used to prevent episodes of high fever, with proven efficacy. [45,47] Zemer's works then highlighted its role not only in the prevention of amyloidosis among this high-risk group, but also in the prevention of impairment of renal functions in patients with pre-established amyloidosis and proteinuria presence[46]. Experiments have also demonstrated that colchicine blocks the production of AA amyloid.[45,47] In light of the results achieved in the treatment of systemic reactive (AA) amyloidosis, some authors have proposed its trial in primary amyloidosis (AL).[47] This proposal was based on the hypothesis that colchicine alters or delays the formation of fibrillar amyloids, or their deposition, based on its interference in the function of macrophages, which appear to participate in the pathogenesis of AL amyloidosis, catabolising the light chains before tissue deposits are formed.[7,10,47,48,49] The various researchers who make use of colchicine have administered it in continual form, over for long periods of time, with doses varying between 0.5 and 1.5 mg/day.[11,18,28,47] However, some have increased it progressively until digestive intolerance is reached.[1,31] Among the references to the use of colchicine therapy in amyloidosis is a study by Cohen. This study compares the survival of a group of AL amyloidosis patients treated with colchicine and the survival of patients suffering from the same disease who were given only supportive care measures. The results show a better survival of the colchicine therapy group (17 months versus 6 months), with the greatest difference seen in women.[47]

Despite the well-known adverse affects of colchicine,[50] the aforementioned studies do not detect significant toxicity.[13,47] leading us to conclude that this therapy is virtually harmless in the proposed doses, even when used for long periods of time.[47] In view of this aspect, and based on the results achieved in individual cases, some authors have proposed the use of colchicine as an adjuvant of the melphalan/prednisone therapy, raising the hypothesis of a synergy between these two treatment regimens.[11,28] As mentioned earlier, the preliminary results of randomized studies point in this direction.[7]

DMSO

Another therapeutic attempt was the use of dimethyl sulfoxide (DMSO). This product has been applied to treat several types of primary and secondary amyloidosis, in both systemic and localized forms, as studies showed its ability to disintegrate fibrillar amyloids in vitro.[51,52] Animal experimentation has proven the disappearance of amyloid deposits in rats under DMSO therapy, followed by the emergence of amyloid-like material in the urine – a phenomenon later seen in pa-

tients with renal amyloidosis.[51] Besides these effects, studies have also observed a decrease in serum SAA levels (the serum factor related to AA protein, part of reactive amyloidosis) and in C-reactive protein (related to the serum amyloid P component), suggesting a reduction of fibrillar amyloid formation.[51] Based on these observations, some positive results have been achieved in patients with amyloidosis secondary to rheumatoid arthritis. However, its use in treating AL amyloidosis has been disappointing, due to the highly variable results and difficult tolerance when administered orally.[7,19,51] There has been a recent description of a sporadic case of response in AL-type pulmonary amyloidosis with DMSO transdermal use.[53]

Others

D-penicillamine has been successfully used in some patients suffering from primary amyloidosis, associated with the melphalan/prednisone regimen.[9,30] The introduction of this medication was based not only on the reduction achieved in immunoglobulin levels,[30,50] but also, and especially, on its hypothetical role in the dissolution of amyloid deposits, complementing the action of the alkylates, as each interferes on a different stage of the amyloidosis chain.[9] In the cases described, no known secondary effects have been observed for this medication.[50] Following the positive results achieved with alpha-tocopherol (vitamin E) in experiments with animals and patients suffering from secondary amyloidosis, Gertz and Kyle tested it in a group of primary amyloidosis patients. Noting that none of the sixteen patients receiving this therapy presented disease regression or an increase in average survival, the authors concluded that this regimen is not useful in treating primary amyloidosis.[18]

An experimental study with animals under amyloidogenic stimulation treated with ascorbic acid (vitamin C) showed a decrease in amyloid deposition. Vitamin C seems to restore the activity of amyloid disintegration, which is present in healthy individuals and reduced in patients suffering from amyloidosis, due to the presence of a serum inhibitor. These findings led to the hypothesis of the clinical use of vitamin C; however, these experimental studies relate only to secondary amyloidosis.[54]

Therapy for organ dysfunctions

Having outlined the regimens used in the primary treatment of AL amyloidosis, some comments are given below concerning the management of dysfunction of certain organs.

Cardiac amyloidosis is a determining condition of poor prognosis in these patients. Besides being a resistance factor to chemotherapy,[10] this condition poses specific hindrances to drugs that are generally used to treat cardiovascular diseases. The maintenance treatment is based on diuretics, but there has been reference to subjective improvement with angiotensin-converting enzyme inhibitors.[4] Cardiac glycosides have the property of binding with fibrillar amyloids, and this binding is associated with an increased toxicity of cardiac glycosides, translating as bradycardia and blocks.[7,55] Beta blockers and calcium-channel blockers have also been associated with a reduction in myocardial function in patients with cardiac amyloidosis. For instance, nifedipine selectively binds with the fibrillar amyloids, resulting in an irreversible binding that is independent of calcium, the very same mechanism described for the digitalis drug.[7,56] These problems assume greater importance because of the use of these drugs in hypertrophic cardiomyopathy, a condition that might be mistaken for cardiac amyloidosis, and is sometimes is only reported with endomyocardial biopsy.[51,55] Complications arising with verapamil and nifedipine were initially reported in cases of hypertrophic cardiomyopathy, in which the patients had elevated left ventricular filling pressure and/or obstruction, parameters identified in the etiology of amyloidosis. In these cases, the resulting hypotension and pulmonary edema may improve after discontinuation of these drugs.[55,57] Although some heart transplantations have been carried out in patients with this condition, the low number of cases and the variable results still hinder the establishment of the role of this intervention in the treatment of cardiac amyloidosis.[4,7]

The literature reports a response to chemotherapy in amyloid nephropathy, with emphasis on cases of nephrotic syndrome. Patients with evolution to renal insufficiency and consequently requiring renal dialysis have short survival rates and poor tolerance to renal dialysis sessions, with frequent episodes of low blood pressure. Transplants have been carried out also in patients with amyloid nephropathy. However, the survival of patients with primary renal injury is higher than that of patients with a transplanted kidney, and the presence of amyloid has been reported in kidneys after transplant.[4]

In relation to alterations in blood coagulation, several cases have been reported of deficit in blood coagulation factors and consequent hemorrhagic manifestations, which have shown response to certain therapy regimens. Several reports show merely transitory and partial response with the use of plasma, concentrates of coagulation factors, or vitamin K.[27,44,58,59] This fact is explained by the rapid absorption of the coagulation factors by fibrillar amyloids, particularly those that exist in the microcirculation of the spleen and liver.[37,59] From this perspective, rapid control of hemorrhage after splenectomy, as mentioned by some authors,[58,59] is understandable, as after the binding sites of the factors are drastically reduced, its plasma activity is increased.[37] Taking the risks into account, this procedure should be considered in the cases of acute hemorrhage resulting from factor X deficit, particularly when there is splenomegaly or hypersplenism, when rapid intervention is necessary,[37,58] For cases in which immediate haemostasis is not required, good results have been reported with the melphalan/prednisone regimen, showing progressive restoration of the activity of the coagulation factors.[37] The results achieved with this association have been justified by the possibility of reducing the amyloid quantity, a fact that has been disputed by some authors.[37,60]

Proposed therapy

Lastly, we would like to suggest the possibility of using alpha-interferon for the treatment of this disease. Like most of the drugs mentioned so far, this substance has also achieved favorable results for the treatment of multiple myeloma, a condition that is closely associated with AL primary amyloidosis, as described earlier.

Alpha-interferon has been used to treat several malignant haematologic diseases, including multiple myeloma, based on its antitumor properties, in particular, its direct antiproliferative activity, immunomodulation capacity, and capacity to modulate oncogene expression.[61,62]

In relation to multiple myeloma, experimental studies have shown that interferon decreases the formation of colonies and self-renewal capacity of the myeloma cells.[63,64,65] One aspect worth noting is its capacity to extend every stage of the cell cycle and, in particular, to accumulate cells in the Go phase, a non-proliferative stage, followed by a decrease in cells transiting to the G_1 phase, a pre-synthesis stage.[61] These alterations might support the use of this drug for maintenance treatment of multiple myeloma following response to cytostatics, or in association with them. When response to cytostatics is observed, the myeloma becomes quiescent, in a stage similar to Go, and the cells become more sensitive to interferon, which, in turn, can extend this phase.[62,66] This type of antiproliferative activity, besides other actions, such as an increase in cytotoxic cells (NK cells) – when used in low doses – and macrophages with tumoricidal function, characterizes interferon as a biological response modifier, not a cytostatic.[61, 62] Several interferon regiments have been clinically trialled in patients with myeloma. Initially, good response was achieved in patients with refractory or relapsing myeloma.[67] Afterwards, interferon started to be used in association with several chemotherapy regimens, such as induction chemotherapy, when an increased response was observed in comparison with other referred regimens, such as melphalan/prednisone and VAD.[68,69] However, one of the greatest achievements of this drug in the treatment of myeloma was observed during the post-chemotherapy maintenance therapy, when the duration of the response and the patients' survival were extended.[66]

Taking into consideration all the aspects mentioned above, and based on the same reasons as those we cited for the administration of cytostatics, we propose the trial of alpha-interferon in patients with AL primary amyloidosis, Thus, when used in association, alpha-interferon can enhance the efficiency of cytostatics and reduce the population of amyloid-producing cells, through its antiproliferative activity and the immunomodulation of natural killer cells. [62] Additionally, some alterations reported with the use of this drug might be of particular interest in the case of primary amyloidosis. One such aspect is the suggestion, following bone marrow studies in patients with multiple myeloma, that the use of alpha-interferon might reduce the secretion of monoclonal proteins by the myeloma cells, instead of their proliferation.[70] This observation is highly relevant because we know that this disease derives from the production of monoclonal light chains with amyloidogenic properties by clonal plasma cells, which do not have the proliferative characteristics of the myeloma.[15,2,23] The use of this substance, therefore, would be more logical than the use of therapies with more tumoricidal effects. Other authors have also shown

the capacity of alpha-interferon to restore the normal immunoglobulin synthesis in patients with multiple myeloma.[71] This is an interesting aspect if we take into account that amyloidosis might derive from abnormal immunoglobulin synthesis.[25] The alterations mentioned above are in line with the hypothesis that alpha-interferon influences the production of protein by the malignant cell clone, a fact that is clearly of relevance in this condition. Another known aspect of alpha-interferon is its higher efficacy in the treatment of myelomas with less tumor mass. Based on the hypothesis of some authors that primary amyloidosis is an early manifestation of myeloma, i.e., before the tumor mass has reached the stage in which it can be generally detected,[15] alpha-interferon would theoretically be more efficient against AL amyloidosis in the absence of multiple myeloma.

During the various studies applying alpha-interferon doses on myeloma, no relevant side effects were reported,[66,69] except for a mild "flu-like syndrome". However, when this symptom appears in patients who are taking melphalan simultaneously, the cytotoxic potential of the latter may be increased.[72]

Used on its own or in association with cytostatics, this substance might be a valid alternative to treat this disease, as it is virtually harmless when administered in the usual doses,[66] it enhances the success of other treatment regimens for multiple myeloma, and it may even be able to interfere in the pathogenesis of AL primary amyloidosis.

Considering the aforementioned aspects, we have used alpha-interferon in three patients with primary amyloidosis, which we had the opportunity to introduce in 1990. [73] Given the small number of cases studies, no conclusions could drawn in terms of survival, but an improvement was observed in some symptoms, such as peripheral polyneuropathy and blood coagulation alterations, coinciding with the periods of drug use.[73,74] Two other patients were also studied.

Subsequently, others have referred to this therapeutic attempt,[75] such as Gertz and Kyle, who recently published their observations on the use of this therapy in a small group of 15 patients, reporting no benefits in relation to traditional regimens.[76]

Conclusions

Although the results to date have not been satisfactory, we believe that some factors might improve the prospects in the management of primary amyloidosis.

On the one hand, early diagnosis of this disease is essential for the efficacy of the therapies, because once the amyloid deposits have resulted in the impairment of vital organs, the prognosis becomes worse, and drugs to reduce amyloid deposition have little influence on the development of the disease. Considering the multisystemic nature of this condition, it is important to know the varied forms of this disease.

On the other hand, the introduction of new methods capable of evaluating the extension of the disease – such as scintigraphy with the amyloid P component marked – can lead to a more accurate analysis of the results achieved through the various regimens trialled, which translates into better defined treatment strategies.

Given the absence of substances capable of reverting pre-established deposits, drugs that can possibly reduce, to some extent, the production of amyloid light chains continue to be the basic therapy for primary amyloidosis. Although the literature in this field refers mostly to the melphalan/prednisone association, we believe that, given the recent results achieved in the treatment of multiple myeloma, other types of chemotherapy regimens, particularly the introduction of alpha-interferon, may be of interest for future lines of research into the treatment of this condition. ■

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