

# Therapeutic options in systemic AL amyloidosis

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## ABSTRACT

Systemic amyloid light chain (AL) amyloidosis is a severe disease with unfavourable prognosis. Since the late 1970s different therapeutic modalities in AL amyloidosis have been investigated, trying to prolong survival. This review deals with the therapeutic modalities in AL amyloidosis to date, and highlights future perspectives.

In AL amyloidosis the precursor protein is a monoclonal immunoglobulin kappa or lambda light chain. In rare cases AL amyloid deposits are localised (e.g. larynx, eyelid, urinary tract) and the underlying monoclonal plasma cell proliferation is thought to be closely connected to the same site. This localised AL amyloidosis is self-limiting and should be treated with local surgery. However, systemic deposition of AL amyloid is far more frequent and in this situation the underlying monoclonal plasma cell dyscrasia is localised in the bone marrow. The plasma cell dyscrasia is often low grade and usually lacks the malignant sheets of immature plasma cells in the bone marrow as in multiple myeloma (MM). However, the accumulation of amyloid fibrils in vital organs leads to organ failure and death. The prognosis of untreated AL amyloidosis is worse than uncomplicated multiple myeloma. Kyle *et al.* found a median survival in untreated AL amyloidosis of 13 months from the time of diagnosis, with considerably shorter

## INTRODUCTION

Systemic amyloidosis is the name of a group of multisystem diseases caused by deposition of insoluble fibrils in organs and tissues, leading to organ dysfunction. Depending on the type of precursor protein of the amyloid fibril, different forms of systemic amyloidosis are recognised.<sup>1</sup> The four main systemic types are shown in *table 1*. AA amyloidosis and AL amyloidosis are the two most frequent.

**Table 1**

*The four major types of systemic amyloidosis based on precursor protein<sup>1</sup> - clinical association and results of tissue analysis with Congo red stain and immunohistology*

TYPE	ASSOCIATION	CONGO RED	IMMUNOHISTOLOGY				
			SAP	κ/λ	SAA	β <sub>2</sub> M	TTR
AL	Plasma cell dyscrasia	+	+	+	-	-	-
AA	Chronic inflammation	+	+	-	+	-	-
Aβ <sub>2</sub> M	Chronic dialysis	+	+	-	-	+	-
ATTR	Familial	+	+	-	-	-	+

SAP = serum amyloid P component, κ = kappa light chain, λ = lambda light chain, SAA = serum amyloid A protein, β<sub>2</sub>M = β<sub>2</sub>-microglobulin, TTR = transthyretin.

median survival for patients with congestive heart failure.<sup>2</sup> The incidence of AL amyloidosis is low (nine per million a year), the median age is 64 years, and it is more frequent in men (male : female = 3:2).<sup>3</sup>

## DIAGNOSIS AND CLINICAL EVALUATION

Diagnosing AL amyloidosis can be difficult due to the insidious nature of this disease, the low incidence, and the various individual clinical features. The main organs involved are the heart, kidneys, liver, and peripheral and autonomic nervous system. Deposition of amyloid in the heart leads to restrictive cardiomyopathy and primary right-sided heart failure, in the kidneys it causes proteinuria and/or renal insufficiency, and in the liver it leads to enlargement and typically to a rise in alkaline phosphatase. Amyloid deposits in the peripheral and autonomic nervous system cause classic polyneuropathy and autonomic neuropathy (e.g. orthostasis). Other features include gastrointestinal tract involvement (leading to constipation, diarrhoea, and/or bleeding), arthropathy, carpal tunnel syndrome and haemorrhagic diathesis. Almost pathognomonic features are macroglossia and periorbital purpura; however, these are present in only 8% of cases. Nearly all patients suffer from malaise and weight loss.

Diagnosis can be made by staining biopsy material with Congo red, giving characteristic apple-green birefringence of eosinophil (red) amorphous material when viewed in polarised light. The most convenient site for biopsy is subcutaneous abdominal fat tissue, aspiration of this fat tissue being a bedside or outpatient procedure of minute's duration. Kyle *et al.* showed that in AL amyloidosis the percentage of positive fat aspiration was 80%. This is comparable with the 75% positive biopsy rate in classic rectum biopsy, a more invasive procedure.<sup>2</sup>

When amyloid is detected, the type of amyloidosis must be established. In AL amyloidosis this can be done by immunofixation of serum and urine to detect kappa or lambda light chain overproduction. Due to the usual low grade of plasma cell dyscrasia this investigation is negative in 10% of patients.

Bradwell *et al.* recently developed a highly sensitive quantitative immunoassay for serum free light chains. This test is much more sensitive for detecting immunoglobulin free light chain than urine testing, and can be used for diagnosis and follow-up after therapy.<sup>4-6</sup> However, care must be taken as patients with non-AL amyloidosis may test false-positive.

Immunophenotyping of plasma cells in bone marrow (kappa : lambda ratio >3 or <1) also points to the presence of a monoclonal gammopathy. In about 40% of cases,

immunohistochemical staining (kappa and lambda) of a Congo red positive tissue specimen may provide additional information regarding the AL nature of the amyloid involved.<sup>7</sup>

At diagnosis, patients often suffer from advanced amyloidosis with involvement and dysfunction of many organs. This limits the therapeutic options. Therefore, once diagnosis of AL amyloidosis has been confirmed, possible organ involvement and organ dysfunction has to be thoroughly investigated with special attention for vital organs. Criteria of clonal and clinical involvement and response to therapy have been proposed by leading groups.<sup>8-10</sup> The most relevant criteria are depicted in *table 2*. An example of classic low-voltage electrocardiography in amyloid cardiomyopathy is shown in *figure 1*.

The extent of organ involvement and organ dysfunction as well as clinical parameters of function, such as WHO performance score and NYHA (New York Heart Association) score of heart failure, are important factors that will be investigated in the current Dutch national HOVON 41 protocol for patients with AL amyloidosis. In Groningen, all patients are also evaluated by serum amyloid P component (SAP) scintigraphy. Radiolabelled SAP is a specific tracer for amyloid and as the localisation of labelled SAP to amyloid does not depend on active deposition it can be used as a quantitative method for imaging amyloid deposits *in vivo*. SAP scintigraphy has a 90% diagnostic sensitivity in AL amyloidosis and is the only method available for serially monitoring amyloid throughout the body.<sup>11-13</sup> *Figure 2* shows an example of such a series in one of our patients.

## THERAPEUTIC OPTIONS

### Precursor-product concept

#### Chemotherapy

A rational therapeutic goal is to reduce or eliminate the precursor protein production, prohibiting further deposition of amyloid fibrils in organs and thereby preventing deterioration of organ function. Given the hypothesis that amyloidosis is a dynamic process of deposition and removal, resolution of amyloid deposits may be expected, enlarged organs may shrink to normal size, and organ function may be restored.<sup>11</sup>

In AL amyloidosis the precursor protein is a monoclonal immunoglobulin light chain. Therefore, the use of chemotherapy, analogous to chemotherapy in MM, is a rational approach.

Alkylating agents such as oral melphalan in combination with prednisolone prolonged survival from 6 to 9 months to 16 to 18 months in a subgroup of patients with AL amyloidosis compared with patients treated with colchicine only.<sup>8,10</sup> Oral melphalan and prednisolone is

**Table 2**

Assessment of vital organ involvement and clonality in AL amyloidosis - some criteria for clinical and clonal responses after therapy

	METHOD OF INVESTIGATION	INVOLVEMENT	RESPONSE
<b>Organ</b>			
Heart	Heart failure history (NYHA I-IV)	NYHA II-IV	Decrease of two classes
	Electrocardiography	Low voltage pattern	
	Echocardiography	Septum thickness >11 mm	Decrease of 2 mm thickness or below 12 mm
	MUGA scan	Ejection fraction <45%	Increase of 20%
	24-hour electrocardiography	Conduction, rhythm, HRV	
Liver	Abdominal ultrasound	Hepatomegaly (span >15 cm)	>2 cm decrease liver span
	Alkaline phosphatase	AP >200 U/l	>50% decrease of AP
	Bilirubin		
Kidney	Creatinine clearance	Clearance <90 ml/min	
	Proteinuria	Proteinuria >0.5 g/day	>50% decrease of proteinuria*
	Serum albumin	Albumin <30 g/l	Increase of >10 g/l
Neuropathy	Clinical examination	Abnormal examination or test	Test response
	Electromyography		
	Orthostatic hypotension		
	Autonomic function test†		
<b>Clonal</b>			
	Serum and urine immunofixation		PR: >50% reduction of clonal protein in serum and urine*
	Bone marrow biopsy	MM or MGUS	CR: disappearance of all signs of monoclonality‡
	Immunophenotyping	Monoclonality	
	Immunoassay free light chain		

NYHA = New York Heart Association scale of heart failure, MUGA = multigated blood pool scan, HRV = heart rate variability, AP = alkaline phosphatase, PR = partial response, CR = complete response, MM = multiple myeloma, MGUS = monoclonal gammopathy of unknown significance.

\*Without being explained by diminishing protein excretion caused by progressive renal failure, †using validated tests based on Ewing and Clark, ‡no monoclonal protein in serum and urine and normalisation of number of plasma cells (<5%) with a normal kappa:lambda ratio in bone marrow.

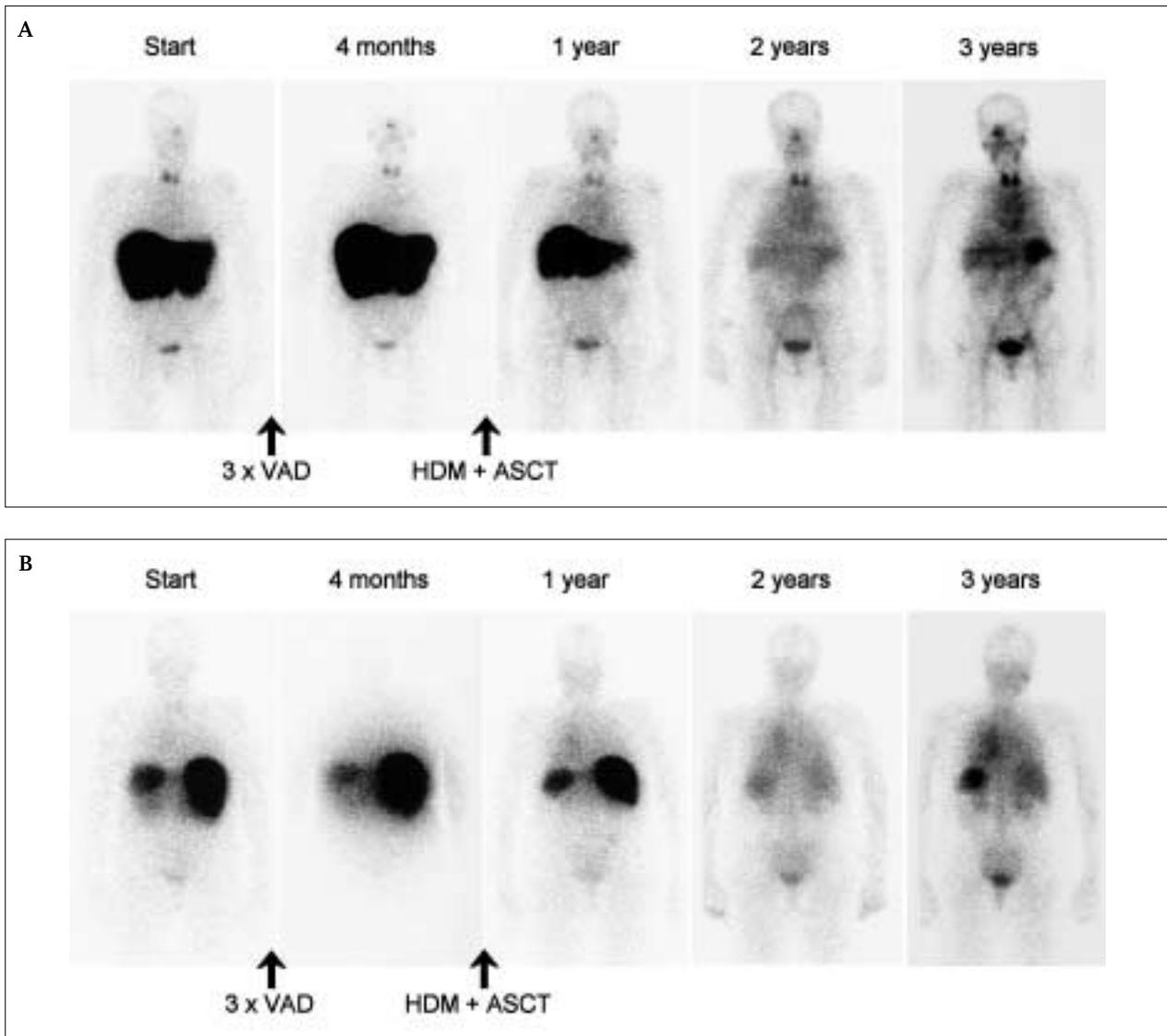


**Figure 1**

Classic electrocardiographic changes indicative of cardiac involvement in a patient with AL amyloidosis: low-voltage and pseudo-antero-septal infarction

effective in only 25% of patients. An important disadvantage of this approach is that it may take months before a clonal and clinical response becomes apparent. Especially patients with rapidly progressive disease may die due to progressive amyloid deposition before they have had the chance to

respond. The addition of colchicine, which inhibits the induction of amyloid in mice and reduces formation of AA amyloid in familial Mediterranean fever, was of no benefit.<sup>8,10</sup> Therefore more aggressive therapies with a much faster effect on precursor-production have been investigated.



**Figures 2A and B**

SAP (Serum Amyloid P component) scans (24 hours after administration of SAP) of a patient with AL amyloidosis who had a partial clonal response to VAD (vincristine, doxorubicin, dexamethasone), HDM (high-dose melphalan), and ASCT (autologous stem cell transplantation) therapy and who had been followed for three years. Clinical response (disappearance of liver enlargement and normalisation of alkaline phosphatase levels) was reflected by serial SAP scintigraphy.

A: Anterior views with intensive uptake in liver at start. After one year, liver uptake diminishes and becomes normal after two years. From two years the normal picture of blood pool activity in heart and major blood vessels and some degradation products in stomach and bladder is visible.

B: Posterior views at the same moments as A. Intensive uptake is present in the liver and also in the spleen at start. Splenic uptake decreases dramatically, although some uptake still remains at the end of follow-up.

In multiple myeloma, VAD (vincristine, doxorubicin, dexamethasone) may induce a quick clonal response in patients with previously untreated and refractory disease.<sup>14,15</sup> Whether VAD is useful in AL amyloidosis is not clear yet. Vincristine often has to be omitted because of the presence of peripheral or autonomic neuropathy and due to its potential cardiac toxicity doxorubicin cannot be used for a long period. In patients with cardiac amyloid involvement

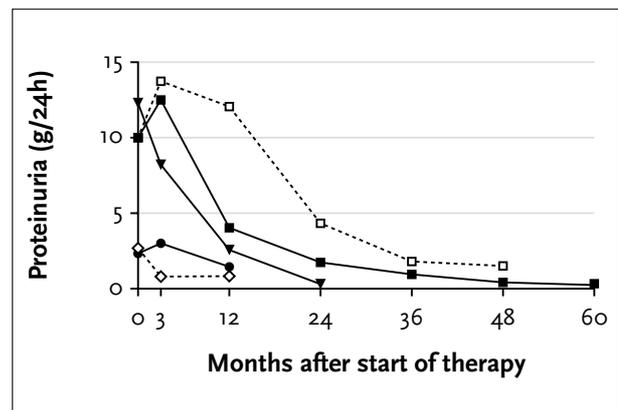
and ejection fraction less than 45%, the dose of doxorubicin should be adjusted or even completely omitted.

In our experience the clonal response to (V)AD used as single treatment is relatively short lived. Nevertheless, (V)AD might be a useful initial approach and this regimen is incorporated in treatment modalities for patients with AL amyloidosis younger than 65 years, as in the currently performed prospective HOVON 41 trial in patients under 66 years.

In the last decade intensive chemotherapy with high-dose melphalan (HDM, 200 mg/m<sup>2</sup>) followed by reinfusion of autologous stem cells (ASCT) has been applied in AL amyloidosis. Five studies reporting more than ten individually described patients with AL amyloidosis actually treated with HDM and ASCT have been published, with a total of 133 patients (table 3).<sup>9,16-19</sup> Recently, Skinner *et al.* published a study of melphalan and autologous stem cell transplantation in AL amyloidosis over an eight-year period (1994 to 2002), using several sequential protocols. Out of 701 consecutive patients with AL amyloidosis, 155 patients were actually treated with HDM and ASCT, 130 of whom had not been described before. Unfortunately, concerning clonal response, clinical response and treatment-related mortality, these 155 patients were not described separately but together with 122 patients who received an intermediate dose of melphalan (100-140 mg/m<sup>2</sup>).<sup>20</sup>

As expected, clonal and clinical responses are closely related. In the three studies in which the relation between both could be retrieved,<sup>9,18,19</sup> clinical response was seen in 28 of 40 patients (70%) who had a clonal response. The remaining 12 patients probably had stable clinical disease, because clinical worsening was not described in any of them. Clonal (complete or partial) response rates vary from 53 to 83%. The study by Skinner *et al.* showed 40% complete haematological response for the group of HDM and IDM treated patients together. Complete haematological response turned out to be positively associated with the dose of melphalan. Noteworthy, a significant survival advantage was noted for patients who achieved complete clonal response, compared with partial clonal response.<sup>20</sup> Clinical response rates vary from 42 to 83%, strongly depending on the time that passed after transplantation. Resolution of amyloid takes time and the rate of resolution of amyloid varies considerably among different individuals. Most responding patients show clinical response after

three to six months (see figure 2), although later responses have been noticed (see figure 3). Importantly, a complete clonal response is not a prerequisite for clinical response and in patients with partial clonal response clinical improvement may still be noticed (see figures 2 and 3). On the other hand, a complete clonal response shows significantly higher clinical response compared with partial clonal response, 66% vs 30%<sup>20</sup> respectively. The equilibrium of formation and regression of amyloid deposits apparently moves towards regression. Noteworthy, the quality of life of responding patients improves, in contrast to patients responding to previously mentioned therapeutic modalities. Treatment-related mortality (TRM) rates are high and vary between 13 and 43%. This is much higher than in MM, where rates below 5% are usually seen. This high TRM is



**Figure 3**  
Monitoring of proteinuria in five patients with AL amyloidosis. All patients are responding to treatment with three courses of VAD (month 0-3) followed by HDM + ASCT (month 4-5). Notice the different pace of regression of proteinuria in time. All patients had partial clonal response.

**Table 3**

Five studies reporting ten or more selected patients with AL amyloidosis actually treated with HDM and ASCT

REFERENCE	YEAR	CENTRE	NUMBER OF PATIENTS	TRM	CLONAL RESPONSE	CLINICAL RESPONSE	CLINICAL RESPONSE (% OF CLONAL)
16	1998	Multicentre	40	15/40 (37%)	18/25 (72%)	14/25 (56%)	ND
17	1998	Multicentre	21	9/21 (43%)	ND	10/12 (83%)	ND
9	1998	Single centre	23	3/23 (13%)	13/20 (65%)	13/20 (65%)	10/13 (76%)
19	2002	Single centre	38	*	20/38 (53%)	16/38 (42%)	13/20 (65%)
18	2002	Single centre	11	2/11 (18%)	7/9 (78%)	6/9 (67%)	5/7 (71%)

HDM = high-dose melphalan (200 mg/m<sup>2</sup>), ASCT = autologous stem cell transplantation, TRM = treatment-related mortality (occurring in the first one to three months after HDM), ND = not described. Clonal and clinical responses were studied in the patients who survived the first three to four weeks after HDM. \*In this study both HDM and IDM (intermediate-dose melphalan) were reported, TRM was only mentioned for the whole group of patients (HDM and IDM together), and not for the patients treated with HDM only.

caused by organ dysfunction in AL amyloidosis. The wide variation of TRM in the different studies is probably due to patient selection, experience, and the conditioning regimen used. Negative prognostic factors are (symptomatic) cardiac involvement and the number of vital organs involved. Especially patients with more than two vital organs affected have a high treatment-related mortality. Therefore careful patient selection for high-dose treatment is essential. Comenzo and Gertz published a risk-adaptive approach in which cardiac involvement and involvement of more than two vital organs were exclusion criteria for ASCT.<sup>21</sup> In the current Dutch study protocol (HOVON 41) and in the study by Skinner *et al.* clinical condition (measured by NYHA score for heart failure and WHO performance score), cardiac status and age are the most important factors in determining whether a patient is suitable for intensive treatment.<sup>20</sup>

Median follow-up in the five individually described studies is 25 months, and median survival has not been reached. Median survival of patients actually treated with HDM and ASCT in the study by Skinner *et al.* is 7.8 years, and five-year survival 61%.<sup>20</sup>

As Dispenzieri *et al.* pointed out, eligibility for stem cell transplantation in AL amyloidosis may be the most important favourable prognostic factor for survival.<sup>22</sup> Selection in this study was strict since Dispenzieri *et al.* retrospectively found only 18% of their patients eligible for HDM and reinfusion of autologous stem cells. In Groningen, 38% of patients were eligible for HDM followed by ASCT between 1985 to 2002. Comparing survival of patients actually treated with HDM followed by ASCT with patients retrospectively eligible for this treatment showed a trend towards better survival in the patients actually treated.<sup>18,20</sup> No prospective study has been performed in which eligible patients treated with conventional therapy (oral melphalan/prednisolone) were compared with patients treated intensively (HDM followed by ASCT).

Since mortality in HDM followed by ASCT is high, intermediate-dose melphalan (IDM, 100 to 140 mg/m<sup>2</sup>) followed by reinfusion of autologous stem cells has been applied. Indeed, treatment-related mortality turned out to be lower (15%) at a cost of lower response rates (25 to 30%)<sup>21</sup> and significantly lower survival of IDM and ASCT vs HDM and ASCT: median survival 2.9 and 7.8 years respectively, and five-year survival respectively 41 and 61%.<sup>20,23</sup> Other chemotherapeutic regimes are anecdotal, such as low-dose intravenous melphalan (25 mg/m<sup>2</sup>, once every four weeks, four to six times),<sup>24</sup> continuous oral low-dose melphalan (4 mg/day, five days a week),<sup>25</sup> or oral cyclophosphamide. The application of allogeneic bone marrow transplantation is also anecdotal.<sup>26</sup>

#### *Thalidomide and other new antimyeloma drugs*

In MM thalidomide has shown to be well tolerated and highly effective in patients resistant to alkylating therapy.<sup>27</sup> The exact antitumour mechanism of thalidomide is still elusive, although antiangiogenesis and immunological effects are thought to be important factors. The limited experience so far with thalidomide in AL amyloidosis has shown a high intolerance, especially oedema, neuropathy, constipation, syncope due to bradycardia, and thromboembolic complications. Therefore, it was withdrawn in 25 to 70% of the patients, and the maximum tolerable dose was often low (below 200 to 300 mg).<sup>28-30</sup> Recently phase II studies with new, potent antimyeloma drugs in patients with MM have been published. The thalidomide analogue (CDC-5013) and the proteasome inhibitor bortezomib (formerly called PS-341) showed promising clinical activity with acceptable toxicity profile in heavily pretreated patients.<sup>31,32</sup> Bortezomib is a novel dipeptic boronic acid, which downregulates *in vitro* the NF-kappaB pathway. *In vitro*, bortezomib has shown potent activity and also enhanced the sensitivity of cancer cells to traditional chemotherapy.<sup>32</sup> Both drugs might be promising in AL amyloidosis in the near future.

#### **Prohibiting formation or stimulating degradation of amyloid fibrils**

To date, there are no drugs available for degrading amyloid depots in tissue, although three drugs are under investigation.

Two trials have been performed with 4'-iodo-4'-deoxydoxorubicin (IDOX), a halogenated anthracycline derivative with significantly reduced cardiac toxicity compared with currently used anthracyclines.<sup>33,34</sup> IDOX can bind to amyloid fibrils, leading to catabolism of amyloid deposits, and has shown to have some effect in soft tissue involvement. The dosing schedule is still under investigation.

Pepys *et al.* are currently investigating R-1-[6-[R-2-carboxypyrrolidin-1-yl]-6-oxohexanoyl]pyrrolidine-2-carboxylic acid (CPHPC).<sup>35</sup> CPHPC blocks the binding sites of serum amyloid P component (SAP) and also cross-links pairs of pentameric SAP molecules. The SAP-CPHPC molecule clearance is high, leading to depletion of SAP from the circulation, and in animal studies reduction of amyloid deposits has been shown.

The third drug, currently being investigated in a multinational phase II/III trial, is sodium-1,3-propane-disulfonate (Fibrillex, or NC-503). In animal studies this low-molecular drug has shown an inhibitory effect on deposition of AA amyloid. Amyloidogenic proteins bind to glycosaminoglycans in tissue, which enhances the process of polymerisation and deposition of amyloid in the extracellular matrix. Fibrillex is a glycosaminoglycan-mimetic drug that competitively binds to the precursor protein SAA, thereby prohibiting the binding to glycosaminoglycans in

tissue.<sup>36</sup> In AL amyloidosis, however, the variety of different precursor proteins (both kappa and lambda) is wide. Therefore the chance is small that one glycosaminoglycan-mimetic drug can be developed that binds to all possible precursor proteins of AL amyloid.

## CONCLUSION

To date, treatment with high-dose melphalan and autologous stem cell transplantation in patients with AL amyloidosis seems to be superior to other forms of (chemo)therapy and therefore should be considered in any patient with AL amyloidosis. Clonal and clinical response rates are high, and survival is prolonged. Due to high treatment-related mortality this therapy is only optional for a subgroup of patients without advanced vital organ involvement, especially of the heart, and good performance status. To increase the number of patients eligible for this treatment, early diagnosis is extremely important.

Patients not eligible for HDM and ASCT could benefit from IDM and ASCT at the cost of lower clonal and clinical response rates and significantly lower survival. Other chemotherapy regimens, such as orally administered melphalan and prednisolone, seem to be less effective but should be tried in patients not eligible for HDM or IDM. So far the role of thalidomide in AL amyloidosis seems to be limited due to high intolerance. New drugs, such as bortezomib and the thalidomide analogues now tested in myeloma, and the development of drugs that are able to resolve amyloid deposits may become important in the near future. Given the low incidence of AL amyloidosis and the potential difficulties in treating patients, treatment should be restricted to or in close collaboration with centres experienced in the management of this disease.

## NOTE

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