Therapy and management of systemic AL (primary) amyloidosis

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Summary

The optimal treatment of immunoglobulin light chain amyloidosis (AL) patients requires early diagnosis, correct amyloid typing, effective treatment and careful supportive therapy. In the last few years the therapeutic arsenal for the management of AL has been considerably enriched. Cardiac dysfunction can be accurately monitored by measuring the serum concentration of natriuretic peptide type-B and cardiac troponins and the quantitative test for circulating free light chains allows an easy assessment of haematological response to chemotherapy. These new tools can be combined in order to maximise the improvement of organ dysfunction and minimise toxicity, adapting the intervention to each patient.

Key words: amyloidosis; diagnosis; treatment

Introduction

Amyloidoses are protein conformation disorders, in which different soluble proteins aggregate as extracellular insoluble fibrils [1]. In immunoglobulin light chain amyloidosis (AL), monoclonal light chains undergo conformational changes leading to their aggregation into amyloid fibrils that can deposit in virtually every organ, with the exception of parenchymal brain tissue [1]. This process causes organ dysfunction and, if it is not halted by therapy, it leads to the patients’ death. Prognosis is determined by the presence and severity of heart involvement and by response to therapy [2].

The optimal management of patients with AL requires early diagnosis, correct amyloid typing, effective treatment, tight follow-up and careful supportive therapy. In the past few years the tools available to the physicians involved in the care of AL patients have considerably improved. New therapeutic regimens can be tailored for each single patient. Cardiac dysfunction can be accurately monitored by measuring the serum concentration of natriuretic peptide type-B (NT-proBNP) and cardiac troponins [3, 4]. A quantitative test for circulating free light chains (FLC) allows an easy assessment of haematological response to chemotherapy [5].

Abbreviations

| AL: immunoglobulin light chain amyloidosis | MP: melphalan plus prednisone |
| ASCT: autologous stem cell transplantation | NT-proBNP: N-terminal pro-natriuretic peptide type B |
| CR: complete remission | PR: partial response |
| FLC: free light chain | SAE: severe adverse events |
| HDM: high-dose melphalan | TDex: thalidomide plus dexamethasone |
| IDM: intermediate-dose melphalan | TRM: treatment-related mortality |
| MDex: melphalan plus dexamethasone | VAD: vincristine, doxorubicin and dexamethasone |

G. P. is partly supported by an investigator fellowship from Collegio Ghislieri, Pavia, Italy
Diagnosis of AL amyloidosis

Systemic amyloidosis should be considered in the differential diagnosis of nephrotic syndrome, left ventricular hypertrophy, hepatomegaly and peripheral and autonomic neuropathy. The organs most frequently involved by AL include kidney (74%), heart (60%), liver (27%) and peripheral (22%) and autonomic (18%) nervous system and in 69% of patients more than one organ is involved at diagnosis [2].

The diagnosis of amyloidosis requires the histological demonstration of the amyloid deposits [6]. The fine-needle aspiration of abdominal fat (sensitivity 87%) is innocuous and can substitute the biopsy of the organs involved. Once the histological diagnosis has been established, the amyloid type should be defined. The characterisation of a biopsy-proven amyloidosis as AL type requires the demonstration of the underlying plasma cell clone. Screening electrophoresis is inadequate, since 56% of patients do not have a detectable monoclonal spike. All patients should have good resolution immunofixation electrophoresis of serum and urine, which can detect a monoclonal protein in up to 97% of patients [2]. The measurement of circulating FLC [5] is a valuable complement of immunofixation and is useful in the follow-up of AL patients after chemotherapy. Although the number of bone marrow plasma cells is often within normal range, a monoclonal plasma cell population can be detected in 84% of AL patients by immuno-fluorescence on a bone marrow aspirate [7]. Finding amyloid deposits in a biopsy in the presence of monoclonal immunoglobulins is strong but not conclusive evidence of AL and the possibility of a monoclonal gammapathy incidentally associated with non-AL amyloidosis should be excluded [8–10]. The mistyping of amyloidosis leads to therapeutic mistakes that may have catastrophic consequences, such as transplanting haematopoietic stem cells instead of the liver. The correct typing of systemic amyloidosis requires a careful clinical evaluation and refined immunohistochemical and genetic testing. The sensitivity of light-microscopy immunohistochemistry in AL is low and at our centre we rely on immunoelectron microscopy that unambiguously characterises the amyloid deposits by co-localising the specific proteins with the fibrils [11, 12]. An alternative approach is the biochemical typing of the amyloid deposits. Genetic testing allows the identification of the specific mutation in the hereditary forms.

Specific therapy

The effective treatments for AL are compared in table 1.

Monitoring the response to therapy

The current therapeutic approach to AL is based on the observation that organ function can be restored if the synthesis of the amyloidogenic precursor is shut down. The aim of therapy is to rapidly reduce the supply of the amyloidogenic monoclonal light chain by suppressing the underlying plasma cell clone, while using supportive measures to sustain the function of the organs involved [13]. A consensus panel from the International Society for Amyloidosis established the criteria for haematological response (table 2).

The United Kingdom National Amyloidosis Centre showed that a >50% reduction of the amyloidogenic FLC (partial remission, PR) is associated with improved survival [14]. More recently, the Mayo Clinic Group reported that survival is predicted by the absolute value of FLC achieved after autologous stem cell transplantation (ASCT) rather than by the percent reduction of FLC [15]. Our group observed that, in patients with cardiac AL, chemotherapy induces a rapid and simultaneous reduction of FLC and NT-proBNP and that

### Table 1

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Clonal response (PR + CR)</th>
<th>CR</th>
<th>TRM (%)</th>
<th>Survival (years)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDM + ASCT</td>
<td>76%</td>
<td>31%</td>
<td>12–11%</td>
<td>7.8</td>
<td>19, 20, 41</td>
</tr>
<tr>
<td>IDM + ASCT</td>
<td>53%</td>
<td>18%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDex*</td>
<td>67%</td>
<td>31%</td>
<td>4%</td>
<td>5.1</td>
<td>28</td>
</tr>
<tr>
<td>HD- Dex</td>
<td>53%</td>
<td>24%</td>
<td>7%</td>
<td>2.6</td>
<td>26</td>
</tr>
<tr>
<td>TDex**</td>
<td>48%</td>
<td>19%</td>
<td>0% (SAE: 65%)</td>
<td>&gt;3</td>
<td>17</td>
</tr>
<tr>
<td>MP</td>
<td>28%</td>
<td>Rare</td>
<td>0%</td>
<td>1.5</td>
<td>25</td>
</tr>
</tbody>
</table>

PR: partial response; CR: complete remission; TRM: treatment-related mortality; HDM: high-dose melphalan; IDM: intermediate dose melphalan; ASCT: autologous stem cell transplantation; MDex: melphalan plus dexamethasone; HD-Dex: high-dose dexamethasone; TDex: thalidomide plus dexamethasone; SAE: severe adverse events; MP: melphalan plus prednisone

* In patients ineligible for ASCT due to advanced disease
** In refractory/refractory patients
complete remission (CR) grants a greater NT-proBNP decrease than PR [16]. Survival of patients in whom FLC and NT-proBNP decrease is significantly prolonged, whereas patients with cardiac AL who do not respond promptly to chemotherapy are at risk of early death [16]. It has been shown that patients who fail to respond to first-line treatment can still benefit from second-line therapy [17]. Thus, the concentration of FLC and NT-proBNP should be measured at least every 3 months, in order to early identify patients who will not benefit from therapy and promptly initiate alternative treatments.

**Stem cell transplantation**

High-dose melphalan followed by ASCT is currently considered the most effective therapy for AL patients who can withstand the procedure. In a retrospective study, patients treated with ASCT had a significant survival advantage over those who received oral melphalan plus prednisone [18]. However, treatment-related mortality (TRM) is high, particularly in patients with heart failure and multi-organ involvement [19, 20]. In 2002, Comenzo and Gertz proposed a risk-adapted reduction of the dose of melphalan used in conditioning, in order to minimise toxicity [21]. However, according to these criteria, of 705 patients seen at our centre, only 82 (12%) would have been eligible for conditioning with high-dose melphalan (200 mg/m², HDM). Also stem cell mobilisation and collection carries significant risks in patients with cardiac involvement and to minimise toxicity it is recommended that only granulocyte colony-stimulating factor be used for mobilisation [22]. Given the modest size of the amyloid clone, pre-transplant cytoreduction with VAD (vincristine, doxorubicin and dexamethasone) or other regimens seems unnecessary. Moreover, pre-transplant treatment with VAD is associated with significant toxicity (TRM 7%) [23] and a randomised trial indicated that the delay associated with debulking allows disease progression [24].

The Boston group started ASCT in 1994 and reported data on 277 patients who were treated up to June 2002 [19]. Conditioning was performed with HDM in 155 patients and with intermediate-dose melphalan (IDM, 100–140 mg/m²) in 122. Complete remission translated into improved survival. Conditioning with HDM was associated with higher CR rate (33% vs 18% on an intention-to-treat basis). Treatment-related mortality was 13%. The Mayo Clinic group reported the outcome of ASCT in 154 AL patients, 103 of whom received HDM and 51 IDM [20]. Haematological response improved survival and was more frequent after HDM than after IDM (76% vs 53%). Overall TRM was 12%.

**Oral melphalan plus prednisone**

The association of melphalan plus prednisone (MP) was standard therapy for AL for a long time and is now offered to poor risk patients. The response rate to MP is approximately 30% and time to response was longer than 1 year in 30% of cases [25]. Although MP is the best tolerated regimen, the long time to response may be unaffordable for patients with rapidly progressive disease.

**Dexamethasone based regimens**

A rapid response to therapy is essential in AL amyloidosis. In multiple myeloma, VAD may induce a quick clonal response. However, this regimen presents serious concerns in AL: vincristine can exacerbate autonomic or peripheral neuropathy, doxorubicin cannot be used in patients with heart failure and the intensive high-dose dexamethasone regimen can cause severe fluid retention or trigger fatal ventricular arrhythmias.

Dexamethasone alone grants a 53% haematological response rate after a median time of 3.4 months, with 24% complete remissions [26]. Treatment-related mortality is 7%. A modified, milder schedule of dexamethasone can induce a response in 35% of patients, in a median time of 4 months [27].

The addition of oral melphalan to dexamethasone (MDex) induces a haematological response in 67% (CR 33%) of AL patients ineligible for ASCT due to advanced disease, in a median time of 4.5 months. Treatment-related mortality is 4% [28]. Haematological response translates into prolonged survival. A French prospective randomized trial compared this regimen to ASCT and showed that transplantation is not superior to MDex in a multicentre setting [29].

**Thalidomide**

Thalidomide is poorly tolerated in AL patients. However, its association with intermediate-dose dexamethasone (TDex) as second-line treatment induces a clonal response in 48% of cases, with 19% CR [17]. Median time to response is 3.6 months. Severe adverse events are frequent (65%), but no treatment-related mortality was reported. Symptomatic bradycardia is a common (26%) re-

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**Table 2**

Criteria for haematological response [6].

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Serum and urine immunofixation negative for monoclonal protein</td>
</tr>
<tr>
<td></td>
<td>Normal free light chain ratio</td>
</tr>
<tr>
<td></td>
<td>Bone marrow plasma cells &lt;5%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>If serum monoclonal component &gt;0.5 g/dL, a 50% reduction</td>
</tr>
<tr>
<td></td>
<td>If light chain in the urine with a visible peak and &gt;100 mg/day and 50% reduction</td>
</tr>
<tr>
<td></td>
<td>If free light chain &gt;100 mg/L and 50% reduction</td>
</tr>
</tbody>
</table>
action to thalidomide in AL and monthly Holter electrocardiogram monitoring is useful in promptly detecting this adverse reaction.

Investigational therapies

New strategies are being developed to attack the plasma cell clone, exploiting the possible graft versus myeloma effect of allogeneic bone marrow transplantation [30] or using the thalidomide analogue lenalidomide or the proteasome inhibitor bortezomib. An alternative is promoting the resorption of amyloid deposits. This could be done by the iodinated anthracycline 4'-ido-4’deoxy-dodoxorubicin that, used at a low, non-myelosuppressive dose, produces an organ response in 15% of AL patients [31]. Amyloid load can also be reduced in mice by passive anti-light chain immunisation [32].

Defining the optimal therapeutic strategy

The availability of several effective therapeutic regimens makes it possible to tailor the treatment strategy for each patient. The goal is a rapid and effective suppression of the synthesis of the amyloidogenic light chain in order to induce a functional improvement of the organ involvement, at the minimum cost in terms of toxicity. The only randomised trial comparing modern therapies is the French Multicentric Trial on ASCT and MDex [29]. This study demonstrated the viability of MDex in AL patients. A limitation of this trial was the multicentre setting that resulted in high TRM when ASCT was performed at centres without a great experience.

Despite there are very few data from randomised clinical trials to support the use of an agent over another, some suggestions can be made. Good risk patients (age <65 years, normal NT-proBNP and cardiac troponins, glomerular filtration rate >50 mL/min) are candidates to ASCT. Conditioning should be performed with HDM (200 mg/m²). Patients who are fit enough to bear dexamethasone based therapy, but who are not eligible for ASCT, can be treated with MDex. However, the exposure to melphalan can jeopardise stem cell mobilisation and patients who present with a potentially reversible contraindication for ASCT should have their stem cell harvested before MDex. Poor risk patients can be treated with MP or included in investigational trials. Refractory and relapsed patients could be treated with TDex.

Supportive treatment

Supportive treatment is a fundamental part of the management of AL patients. It is aimed at maintaining the quality of life and prolonging survival, whilst specific therapy has time to take effect. The mainstay of the treatment of congestive heart failure and nephrotic syndrome in amyloidosis are salt restriction and judicious diuretic use [13]. Cardiac function in amyloidosis is often preload dependent and reduction of intravascular volume should be avoided, particularly in patients with hypoproteinaemia and postural hypotension. Most patients with AL have asymptomatic autonomic nervous system involvement [33] and hypotension can easily ensue after treatment with angiotensin-converting enzyme inhibitors that should be used with great caution and at the lowest effective dose. Patients with recurrent syncope may benefit from pacemaker implantation. Patients who present repetitive ventricular arrhythmias at 24-hour Holter electrocardiogram are at risk of sudden death [34] and may benefit from treatment with amiodarone. The utility of implantable defibrillators is controversial. End-stage renal failure is treated with dialysis.

Hypotension is present in almost 20% AL patients and is exacerbated by heart failure and hypoproteinaemia. Patients can benefit from fitted elastic leotards and midodrine [35], whereas fluocortisone is poorly tolerated due to fluid retention. Neuropathic pain benefits from gabapentin or pregabalin treatment. Diarrhoea due to gastrointestinal and/or autonomic nervous system involvement can be controlled with octreotide [36].

More than 50% of AL patients experience an unintentional weight loss and more than 20% are malnourished [37]. Low serum prealbumin concentration and body mass index are independent prognostic factors for survival [37] and maintenance of a good nutritional status should be an integral part of supportive therapy.

The transplantation of the organs involved by amyloidosis may prolong survival and render patients with advanced disease eligible for aggressive specific treatment. The main concerns with organ transplantation are recurrence of amyloidosis in the graft and progression in other organs in patients who do not respond to chemotherapy. Organ transplantation may be an option in patients who attained CR, but have irreversible organ damage. Cardiac, renal and liver transplantations can also represent a viable option before chemotherapy, but they should be immediately followed by effective anti-clone therapy [38–40].
Conclusion

The availability of several effective treatment options and the possibility of accurately monitoring the disease with the biochemical markers of haematological response and cardiac function have rendered AL a manageable disease. The median survival of AL patients seen at our centre is approaching four years [2] and 23% of patients survive more than 10 years. Still, 15% of patients die within 6 months from diagnosis and a well tolerated and rapidly effective therapy is urgently needed for poor-risk patients. Moreover, an increased awareness of the clinical features of the disease on the part of the physician is still needed to achieve an early and correct diagnosis.

References

7. Lachmann HJ, Gallimore R, Gillmore JD, et al. Improving awareness of the clinical features of the disease on the part of the physician is still needed to achieve an early and correct diagnosis.

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SWISS MED WKLY 2006;136:715–720 · www.smw.ch


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