Current therapeutic possibilities in primary and secondary amyloidosis and our experience with 31 patients

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Abstract

Primary (AL) and secondary (AA) amyloidosis are systemic diseases characterized by a process of amyloid deposition in many organs with unsatisfactory survival of patients. Apart from surgical intervention in those patients with bronchiectasias or osteomyelitis, the possibilities of influencing the development of AA amyloidosis are limited. The milestone therapy in patients with rheumatic diseases includes early treatment with DMARDs (disease-modifying antirheumatic drugs). A new promising therapeutic alternative is represented by anti-tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) drugs such as infliximab and etanercept. The last class of agents used in the treatment of AA interferes with fibril formation: iododoxorubicin and low molecular weight sulfates (fibrilex). In the group of patients with AL, in addition to the standard combination of melphalan and prednisone, other therapeutic approaches such as ASCT (autologous stem cell transplantation) and new drugs with different mechanisms of action have been added recently. For the future, we can expect the development of immunotherapy (both active vaccination and passive immunization). In our department, we have treated 17 patients with AL and 14 patients with AA amyloidosis since 1995. We used various treatment regimens in both groups of patients. The treatment stabilized the disease or achieved partial remission in only 36% of patients with AA amyloidosis despite the use of intensive therapeutic modalities, while in the AL group a response was achieved in 82% of patients. ASCT improves patients survival in AL amyloidosis, but strict selection criteria are necessary (less than two affected organs and no signs of myocardial dysfunction).

Keywords: AA amyloidosis; AL amyloidosis; amyloid; ASCT; DMARDs; immunotherapy

Introduction

Primary (AL) and secondary (AA) amyloidosis are systemic diseases characterized by a process of amyloid deposition in many organs, leading to organ dysfunction. If untreated, the median survival is \(\sim\)13 months in the group of patients with AL; 51% of patients survive \(>\)1 year and only 16% survive \(>\)5 years [1]. In AA, 50% of patients survive \(>\)4 years and only 25% survive \(>\)10 years [2].

Apart from a surgical intervention in those patients with bronchiectasias or osteomyelitis, and colchicine treatment in patients with familial Mediterranean fever, our possibilities of influencing the development of AA amyloidosis are limited. The milestone therapy in patients with rheumatic diseases includes early treatment with disease-modifying antirheumatic drugs (DMARDs), i.e. cyclophosphamide, methotrexate, chlorambucil, salts of gold, penicillamine, sulfasalazine, cyclosporin A and azathioprine [3]. The new promising therapeutic alternatives are drugs such as lefunomide (inhibitor of pyrimidine synthesis in T lymphocytes), infliximab [chimeric monoclonal antibody against tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\))] and etanercept (soluble receptor for TNF-\(\alpha\)). The last class of agents used in the treatment of AA interfere with fibril formation: the anthracycline derivate iododoxorubicin (a positive effect on soft tissues such as tongue, skin and genitals, but only a mild effect on parenchymal organs such as liver, kidneys and spleen) and the low molecular weight sulfate, fibrilex [4]. Allogenic bone marrow transplantation can be performed in patients with resistance to the standard treatment regimens.

Since AL amyloidosis develops as the result of a neoplastic expansion of the plasma cell population
synthesizing the amyloidogenic light chains, the primary therapeutic target remains the clone. To the standard therapeutic combination of melphalan and prednisone, new drugs with different mechanisms of action have been added: high-dose dexamethasone, VAD (vincristine, adriablastine, dexamethasone) or C-VAD (cyclophosphamide + VAD), iododoxorubicin, and high-dose melphalan in combination with autologous stem cell transplantation (ASCT) [5,6]. This promising therapy has many problems such as the optimal selection of eligible patients and very high transplant-related mortality. Survival of patients with AL without signs of multiple myeloma undergoing ASCT is prolonged (in an adequately selected cohorts of patients) to 46 months compared with 13 months in untreated patients [7]. Newer therapeutic approaches include blockade of TNF-α, thalidomide [blockade of TNF-α, vascular endothelial growth factor (VEGF) and NF-κB] and anti-CD20 antibody rituximab (blockade of plasma cells). These drugs at present are undergoing various stages of clinical trials [8].

For the future, we can expect the development of immunotherapy, both active vaccination and passive immunization. This type of treatment develops rapidly, especially in AL amyloidosis. Fragments of light chains or dendritic cells are used as antigen in active vaccination [9]. Passive immunization with amyloid-reactive antibody can be used in severe forms of AL amyloidosis as rescue and is a relatively low toxicity treatment possibility.

Patients and treatment regimens

We have treated 17 patients with AL and 14 patients with AA amyloidosis in our department since 1995. The mean age was 59.2 years in the AL group at the time of diagnosis, and the underlying diseases are given in Table 1. The kidneys were affected in all patients, the heart in 59% of patients, liver, joints and skin in 26% of patients, and polyneuropathy was detected in only one patient. Nine patients were treated with a combination of melphalan (at a dose 0.1mg/kg/bw) and prednisone (0.8mg/kg/bw) for 4 days every 4 weeks, two patients were treated with high-dose dexamethasone (40mg/4 days/three times monthly), four patients underwent ASCT with high-dose melphalan (three patients with myeloma and one patient with MGUS—monoclonal gammopathy of undetermined significance; melphalan was given at a dose 200mg/m²), and two patients were treated with another protocol (VCMP/VBMP combination).

The mean age was 58.1 years in the AA group at the time of diagnosis and the underlying diseases are given in Table 1. Kidneys were affected in all patients, and the heart and bowel in 36% of patients. Two patients were treated with corticosteroids at various doses, 10 patients with a combination of corticosteroids and DMARDs (methotrexate in three patients, cyclophosphamide in seven patients, azathioprine and chlorambucil in one patient and cyclosporin A in three patients; in some patients, the treatment was changed if the disease progressed). A patient with natural killer cell deficiency was treated with transfer factor and long-term antibiotic therapy, and in one woman no treatment was given due to her recent history of active tuberculosis.

Table 1. Underlying diseases in the groups of patients with AL and AA amyloidosis

<table>
<thead>
<tr>
<th>Type of amyloidosis</th>
<th>Underlying disease</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Multiple myeloma</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>MGUS</td>
<td>8</td>
</tr>
<tr>
<td>AA</td>
<td>Rheumatoid arthritis</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Juvenile chronic arthritis</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ankylosing spondylitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Relapsing fasciitis</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Abscesses in NK cells deficiency</td>
<td>1</td>
</tr>
</tbody>
</table>

MGUS, monoclonal gammopathy of undetermined significance; NK, natural killer.

Results

Progression of the disease was detected in three patients with AL (17.6%), stable disease was found in five patients (29.4%), and in nine patients (53%) we achieved partial remission of the amyloidosis. For remission/response, we have used criteria described by Merlini et al. [10]. Median survival of 13 months in the whole AL group was prolonged to 14.5 months in patients after ASCT. Progression of the disease was detected in nine patients (64.3%) with AA, stable disease was present in three cases (21.4%) and only in two patients (14.3%) did we achieve partial remission of AA amyloidosis. Median survival was 30 months in this group of patients.

Discussion

Therapeutic efforts in patients with AL amyloidosis have been directed primarily at reducing the synthesis of the amyloid light chain precursors.

In one of the largest studies, published by Kyle et al. [11], the median survival was 13 months in untreated patients with AL amyloidosis; treatment with combination of melphalan and prednisone prolonged the survival only to 17–18 months. Survival reaches up to 46 months in the group of patients treated with ASCT [7]. Achievement of good results is influenced mainly by reduction of the high peri-transplant mortality described by many authors. This mortality even reached 37.5% in one study [12]. It seems to be clear that strict criteria for patient selection should be adopted. The following patients are good candidates for ASCT: two or less affected organs, no cardiac involvement, glomerular filtration rate > 51 ml/min and no signs of multiple myeloma.
Patients with AL who have more than two major organs involved or who have advanced cardiomyopathy are at high risk of dying within the peri-transplantation period [13]. We are not able to provide any recommendations from our results due to the limited number of treated patients. Very short survival time (14.5 months) in our group of patients is probably caused by suboptimal selection of patients for ASCT (three out of four had multiple myeloma) and multiorgan involvement at the time of diagnosis. One patient died 3 months after ASCT due to cardiac failure, and one patient died due to gastrointestinal bleeding 5 months after ASCT.

Survival of our patients with AA amyloidosis is also unsatisfactory. The main cause is probably the delayed referral of patients to our centre, when massive infiltration of tissues by amyloid was already present. It is practically impossible to influence the disease at this advanced stage despite the use of intensive treatment.

**Conclusion**

Both forms of acquired systemic amyloidosis, AL and AA, represent severe diseases with a limited response to treatment and an unsatisfactory prognosis. Only early identification of the disease and aggressive treatment could lead to remission.

In our groups of patients, the treatment stabilized the disease or achieved partial remission in 36% of patients with AA amyloidosis despite the use of intensive therapeutic modalities. In the AL group, the response was achieved in 82% of patients. ASCT can improve patient survival in AL amyloidosis, but strict selection criteria are necessary.

**References**