Adapting to AL amyloidosis

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An article by Perfetti *et al*. in this issue of the journal is an examplar of the progress made in the last 15 years in the treatment of the clonal hematologic disease AL amyloidosis. The use of chemotherapy and immunomodulatory therapy have changed AL amyloidosis from a uniformly fatal disease to one in which many patients can achieve partial or complete hematologic remissions, accompanied by improvement in organ function, quality of life, and survival. Because of the availability of disease-remitting treatment, we practicing hematologists need to adapt our clinical practice to be aware of the protean manifestations of the disease, make use of new assays for molecular diagnosis and staging, and initiate treatment to allow our patients to adapt and live with, or conquer, this previously fatal disease.

Perfetti *et al*. describe results of a risk-adapted approach to the use of high-dose melphalan and autologous peripheral blood stem cell transplantation for the treatment of AL amyloidosis.[1] *Starch-like* amyloid deposits in tissues were first described by Virchow, but it has taken 150 years to identify the biochemical nature of these deposits, determine their etiology, and develop effective treatments. Progress in this has accelerated in recent years, and will be reviewed here.

The systemic amyloidoses are a group of diseases caused by misfolded proteins that deposit outside of the central nervous system. These comprise three major categories of diseases. The first is secondary amyloidosis, occurring in the setting of chronic infection or inflammation that leads to increased production of acute-phase reactant proteins in the liver. Among these liver-derived proteins is serum amyloid A protein, the precursor for AA amyloid (each of the amyloidoses is abbreviated based on the type of the amyloid precursor protein). The second category includes the hereditary amyloidoses. Many of these are due to amyloid-prone polymorphisms of the transthyretin (TTR) gene. TTR, a transport protein for thyroxine and retinol binding protein, is also produced in the liver. Inherited mutations, particularly common in populations in Portugal, Scandinavia, and Japan, can lead to familial amyloiodotic cardiomyopathy (FAC) or familial amyloiodotic polyneuropathy (FAP). The V122I mutation of TTR occurs in nearly 4% of the African American population and has been postulated to contribute to the increased rate of cardiomyopathy in that population. Hereditary amyloidoses can also be due to polymorphisms or mutations of fibrinogen, apolipoproteins, lysozyme, gelsolin, and other proteins. An interesting variant of the TTR diseases is so-called *senile systemic* or *senile cardiac* amyloidosis, in which wild-type TTR can form fibrillar deposits, usually in the hearts of males over 70 years old. This highlights the fact that the formation of amyloid is an inexorable consequence of aging, occurring in the brain as Alzheimer's disease and in the body as senile amyloidosis.

The third category of systemic amyloidosis is termed primary, referring to the immunoglobulin (Ig) light chain (LC) amyloidoses, or AL. AL can occur along with any clonal lymphoid disease in which Ig is secreted, including non-Hodgkin's lymphoma, Waldenström's macroglobulinemia,[2] and plasma cell dyscrasias such as multiple myeloma and AL amyloidosis itself.

Each of these categories of disease now has effective treatments. AA amyloidosis can be ameliorated by effective treatment of the underlying infection or inflammation, but recently, an anti-fibril agent, eprodisate (Kiacta, formerly Fibrillex), has shown efficacy in phase III trials for the treatment of AA amyloidosis (*Dember et al., personal communication*). For ATTR amyloidosis, orthotopic liver transplantation provides an organ-based mode of *gene therapy*, as the major site of synthesis of the mutant TTR is replaced with a source of wild-type TTR; because the disease onset is so prolonged, the mutant TTR-secreting liver can even be used in a *domino* transplant as a donor organ for patients with other forms of liver disease. For AL amyloidosis, effective chemotherapy and immunomodulatory therapies can induce prolonged and complete remissions of the disease. Thus, there is now an increased incentive for physicians to make a timely diagnosis of amyloidoses and develop an appropriate treatment plan.

Pathogenesis

Amyloid diseases occur through a process of protein aggregation that produces ordered polymers that form protofilaments and then fibrils. These fibrils, regardless of the type of precursor protein, are about 10 nm in diameter and have a similar appearance by electron microscopy, atomic force microscopy, and circular dichroism. They stain with dyes such as thioflavin T and Congo red, the latter producing a characteristic apple green birefringence when visualized under polarized light microscopy.

Current theory suggests that tissue damage in the amyloidoses occurs through multiple mechanisms. It is not only the end-stage fibrillar deposits that produce disease since it is believed that oligomeric precursors

that form doughnut-like ring structures can interact with and damage cells; these rings may even insert into membranes.[3] Evidence that such precursors are toxic comes from clinical observations that organ function can improve acutely after treatment of amyloidosis, in a time frame that is believed to be too short for resorption of fibrillar deposits. For example, levels of N-terminal pro-brain natriuretic peptide (BNP), a marker of cardiac stress, can drop soon after chemotherapy.[4] Thus, treatment is targeted at reducing production of the precursor protein and the oligomers formed from it, as well as at reducing the formation of the fibrils themselves.

In AL amyloidosis, the Ig LC are produced by clonal lymphocytes, or more frequently plasma cells, which secrete more Ig. This occurs in 10-20% of cases of multiple myeloma, which is a true plasma cell neoplasm. However, in the majority of cases of AL amyloidosis, only a low grade plasmacytosis in the bone marrow, usually 5-15% of the nucleated cells, leads to the disease. It is controversial whether these cells are expanded in the marrow due to acquisition of mutations comparable to those in multiple myeloma or not; it has also been theorized that antigens may drive the expansion of these cells. Abnormal plasma cells are believed to synthesize heavy and light Ig chains in an unbalanced fashion, leading to the occurrence of *free* light chains in the circulation; an assay has been developed to detect these. They may also occur through dissociation of heavy and light chains, and LC may be post-translationally modified, proteolytically processed, or associate with other specific serum components, such as serum amyloid P (SAP) component, to initiate the process of fibrillization and deposition.

Clinical presentation

Patients with the bone marrow disorder AL amyloidosis usually come to the attention of non-hematologists first. Although non-specific complaints such as fatigue and loss of appetite or taste are common, the types of symptoms that lead to testing for amyloidosis relate to the organ impairment caused by the disease (Table 1). Commonly, patients with nephropathy develop peripheral edema; patients with cardiomyopathy develop symptoms of congestive heart failure due to diastolic dysfunction or arrhythmias; patients with autonomic neuropathy develop orthostatic changes in blood pressure or have symptoms of gastrointestinal dysmotility. Patients may develop peripheral neuropathy in the absence of diabetes or vascular disease. Patients with involvement of soft tissues can develop pathognomonic macroglossia or arthropathy. Patients with capillary involvement can have easy bruising, particularly around the eyes in response to coughing or minimal trauma, producing the *raccoon eye* appearance. Bleeding is exacerbated by deficiency of clotting factor X, which can be specifically adsorbed to amyloid deposits.[5] The presence of any of these constellations of symptoms and signs should initiate the work-up described below.

Table 1. Clinical syndromes in which AL amyloidosis should be suspected.

Nephrotic syndrome, hypoalbuminemia
Cardiomyopathy
Diastolic dysfunction
Increased wall thickness
Low voltage electrocardiogram
Autonomic neuropathy
Orthostatic hypotension
Gastrointestinal dysmotility
Peripheral neuropathy
Absence of diabetes mellitus, vascular disease
Microvascular hemorrhage
Periorbital ecchymoses*
Factor X deficiency
Soft tissue deposits
Macroglossia*
Muscle or joint involvement

**Pathognomonic for AL amyloidosis.*

Table 2. Laboratory tests for the diagnosis and staging of AL amyloidosis.

Screen for amyloid deposits by Congo red staining
Abdominal fat aspirate
Involved organ biopsy
Labial salivary gland biopsy
Screen for monoclonal gammopathy
Serum protein electrophoresis (insensitive)
Serum immunofixation electrophoresis
Serum nephelometric free light chain assay*
Serum quantitative immunoglobulin measurement
Urine immunofixation electrophoresis
Urine nephelometric free light chain assay*
Urine κ/λ quantification
Screen for plasma cell dyscrasia
Bone marrow immunohistochemistry for CD138, κ, λ
F low cytometry for CD138, κ, λ
Screen for renal involvement
Measurement of daily urinary protein excretion
Creatinine, creatinine clearance
Screen for amyloid heart disease
Electrocardiogram
Measurement of BNP, pro-BNP, or troponin
Echocardiogram or magnetic resonance imaging
Event monitoring for arrhythmia, if clinically indicated
Screen for neuropathy
Orthostatic changes in blood pressure
Peripheral neuropathy by examination
Screen for gastrointestinal involvement
Stool occult blood
Endoscopy, if clinically indicated
Assessement of liver and spleen size
Screen for coagulopathy
PT, PTT, factor X
Screen for pulmonary or pleural involvement
Chest X-ray
Pulmonary function testing, if clinically indicated

**Freelite™ chain assay, The Binding Site, Inc.*

Diagnosis

The diagnosis of AL amyloidosis rests upon two pillars: the demonstration of amyloid deposits, and evidence that the deposits are derived from clonal Ig LC (Table 2). Amyloid deposits are generally identified by Congo red staining and examination under polarized light, which produces the characteristic apple green birefringence; under visible light, waxy pink staining is seen. Ten-nanometer fibrils can also be identified by transmission electron microscopy. Tissue for staining can be derived from the bone marrow itself, adipose tissue obtained from the abdominal wall by aspiration after local anesthesia, or by biopsy of the involved organ. In the center at Pavia, the salivary glands are also biopsied, although this procedure is not widely practiced in the USA. Gingival and rectal biopsies are rarely necessary any longer.

For demonstration that Ig LC are the cause of the disease, one must search carefully for evidence of a clonal plasma cell dyscrasia, and multiple tests, not a single test, must be done. Testing includes a bone marrow biopsy with immunohistochemistry or flow cytometry to identify a clonal LC population and immunofixation electrophoresis (IFE) of serum and urine. Standard serum protein electrophoresis (SPEP) often fails to demonstrate a significant paraprotein M-component, and urine protein electrophoresis (UPEP) frequently demonstrates albuminuria rather than Bence Jones proteinuria, thus, SPEP and UPEP are not useful screening tests. Recently, a quantitative nephelometric assay for free Ig LC in the serum has been developed, which is useful for screening and monitoring treatment responses.[6,7] Many investigators seek to definitively demonstrate the clonal LC in the amyloid deposit using immunohistochemical or immunoelectron microscopic techniques, particularly in clinically ambiguous cases, which have features of AF or AA as well as AL. In some cases, excluding these by genetic or immunohistochemical testing is as important as ruling in AL.

Diagnostic testing in cases of AL amyloidosis must also include a careful evaluation of end-organ function. This involves testing of diastolic and systolic cardiac function and rhythm, assessment of renal function and proteinuria, screening for symptoms of autonomic and peripheral neuropathy, exclusion of erosive amyloid enteropathy, and screening for coagulopathy due to factor X deficiency. Recently, an international consensus of definitions of organ involvement and responses to treatment has been developed.[8]

Risk-adapted treatment options

Melphalan-based chemotherapy

The mainstay of treatment for AL amyloidosis for the past 15 years has been melphalan-based chemotherapy. Melphalan is effective for plasma cell diseases, and has minimal organ-specific toxicity. Randomized trials showed a survival benefit for patients treated with melphalan and prednisone taken in monthly oral pulses.[9,10] More recently, intensification of the steroid regimen with a combination of melphalan and dexamethasone has been reported to increase the hematologic remission rate.[11] Likewise, intensification of the melphalan dosing with high dose intravenous regimens supported by autologous stem cell transplantation (HDM/SCT) produces a higher rate of hematologic responses,[12,13] although AL amyloidosis patients have much more toxicity from this and all other treatments. Nonetheless, HDM/SCT appears to produce the most durable remissions and highest likelihood of improved organ function[14] and quality of life.[15] Thus, experienced centers continue to refine the criteria by which patients are selected for such treatment, adjust melphalan dosing, and optimize supportive care. Based on these strategies, a *risk-adapted* treatment approach has been proposed.[16] The study described in this issue of the journal is the first to establish strict criteria and apply them prospectively in the context of a single study.[1] Low risk patients were less than 60 years old, had no more than two visceral organs involved, had a cardiac ejection fraction greater than 50%, a normal level of creatinine, a diffusing capacity of the lung more than 50% of predicted, and minimal impairment of performance status; these patients were treated with 200 mg/m^2 IV melphalan. Patients over the age of 65, with more than three organs involved, NYHA heart failure classification III or IV, bilirubin greater than 2 mg/dL, systolic blood pressure less than 90 mmHg, reduced lung diffusing capacity, or poor performance status were considered high risk, and not offered HDM/SCT. Patients with intermediate features and risk were treated with lower doses of intravenous melphalan (140 mg/m^2, or 100 mg/m^2 if NYHA heart failure class II). Other experienced centers use similar criteria for selecting appropriate patients for HDM/SCT and adjusting melphalan dosing. In 22 consecutive patients, results were excellent, with 14% treatment-related mortality, a hematologic response rate of 55% (complete, 36%; partial, 19%) by intention-to-treat analysis, and organ responses in 75% of patients. The median survival for this group was 68 months. These results reinforce the safety and efficacy of the HDM/SCT approach, when applied selectively and with care. Recently, we have reported that HDM/SCT can even be used judiciously and effectively in patients over the age of 65.[17]

HDM/SCT has recently been compared to the oral melphalan-dexamethasone regimen in a randomized multicenter trial carried out in France. Based on results presented in abstract form at the American Society of Hematology meeting in 2005, there was no difference between the two arms. However, the early mortality rate in the transplant arm was so high that any positive long-term effect of HDM/SCT was markedly attenuat-

ed. This study does not settle the question of which treatment is superior, but does highlight the need to treat patients with AL amyloidosis in a highly individualized, risk-adapted fashion as described,[1] with components of the evaluation and treatment performed at centers familiar with the disease.

Immunomodulatory therapy

The well-demonstrated activity of corticosteroids in plasma cell diseases has prompted development of other immunomodulatory agents for AL amyloidosis as well as multiple myeloma. The lower bone marrow burden of plasma cells may make AL a more inviting target for such approaches, including active vaccines, passive immunotherapy, or non-specific immunomodulation. The first attempt to build upon the corticosteroid platform was a multicenter trial of α-interferon along with dexamethasone, which led to complete hematologic responses in 24% of evaluable patients, organ improvement in 45% of patients, and a median survival of 31 months.[18] Unfortunately, as is the case for all therapies for AL amyloidosis, tolerance was poor, with only two-thirds of patients receiving the planned three cycles of dexamethasone induction and the 2-year interferon maintenance program was delivered for only a median of 7 months. Subsequent studies have substituted thalidomide and lenalidomide for interferon, based on promising results in multiple myeloma and indications that these drugs may affect plasma cell diseases in multiple ways. Thalidomide was not well-tolerated in two studies,[19,20] but two other studies in press in *Blood* indicate that the combination of lenalidomide and dexamethasone produces a high rate of hematologic responses and improvement in organ function, with moderate but manageable toxicities.[21,22]

Anti-fibril therapy

In addition to reversing the underlying plasma cell disorder, a goal of treatment in the amyloidoses is to prevent or reverse the toxicity of oligomeric amyloid aggregates and fibrils. The first drug to do this effectively is eprodisate (Fibrillex), a compound that disrupts glycosaminoglycan binding to amyloid fibrils and significantly delays the progression of renal failure in AA amyloidosis. The compound R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) binds to the accessory molecule serum amyloid P (SAP) component and reduces its level in the serum,[23] but has not been shown to affect amyloid deposits in humans. For AL, the compound 4'-iodo-4'-deoxydoxorubicin (IDOX), an analog of the chemotherapy agent doxorubicin, disaggregates fibrils in both *in vitro* and *in vivo* models,[24] but has also not yet been proven to be efficacious in early clinical trials.[25] Thus, we continue to search for compounds that work in patients to interrupt the underlying pathogenic mechanisms of the amyloid diseases, with great hope that such compounds will eventually be found and developed for clinical use in our patients.

Supportive care

For any treatment approach for AL amyloidosis to be effective, the hematologist and the patients themselves are dependent upon optimal management of the organ impairment induced by the disease. Regardless of the specific treatment directed against the plasma cell dyscrasia, supportive care to decrease symptoms and support organ function plays an important role in the management of this disease and requires the co-ordinated care by specialists in multiple disciplines. The management of heart failure, kidney failure, and autonomic neuropathy in these patients is highly complex. Many of the drugs used for organ disease due to other processes are ineffective or deleterious in AL amyloidosis. Some examples of this include the contraindication to the use of digoxin in amyloid cardiomyopathy, because of specific binding to amyloid fibrils and a high incidence of toxicity even at normal serum levels, and the relative contraindication to the use of beta blockers and calcium channel blockers, which are poorly tolerated in the setting of diastolic dysfunction. The amyloid kidney is exquisitely sensitive to nephrotoxins, including aminoglycosides and intravenous contrast dye. Autonomic neuropathy can be disabling and may respond to the use of α-agonists or mineralocorticoids, or physical measures to support the blood pressure. Readers are referred to other sources of information on this complex subject.

Conclusions

As highlighted in the article by Perfetti *et al*. in this issue of Haematologica,[1] we have come far in the treatment of AL amyloidosis, but more remains to be accomplished. General medical practice needs to adapt to be alert to the protean clinical manifestations of systemic amyloid diseases and initiate appropriate consultation and subspecialty evaluation. Hematologic practice must adapt to new and more accurate molecular diagnostics and to the presentation of appropriate treatment options for our patients. Physicians and patients should continue to support basic and clinical research into the mechanisms of disease in the amyloidoses and clinical trials to improve treatment options. Working together, we must strive to find effective treatment for each and every patient diagnosed with this previously untreatable and devastating disease.

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