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Modern Treatment of Amyloidosis: Unresolved Questions

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ABSTRACT

During the past 10 to 15 years, there has been substantial progress in developing new treatments for the systemic amyloidoses. These advances have improved patient outcomes but have also raised new questions with direct clinical implications. For example, development of less intensive treatments for AL amyloidosis has made less certain the role of autologous stem cell transplantation, and new quantitative assays should now allow determination of the importance of fully eliminating amyloidogenic light chain production in AL disease. Additionally, observations from a clinical trial in AA amyloidosis have generated hypotheses about the relative contributions of amyloid precursors and mature fibrils to amyloidosis-associated kidney disease.

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The systemic amyloidoses are rare disorders that frequently involve the kidneys.[1] Historically, the amyloidoses were considered untreatable and uniformly fatal diseases. Development of new treatment approaches has improved the outlook for many individuals with these disorders; however, with these advances come new questions. The purpose of this article is to discuss unresolved questions in amyloidosis that have implications for treatment.

WHAT IS THE BEST INITIAL TREATMENT FOR AL AMYLOIDOSIS?

AL amyloidosis is the most common and most rapidly progressive type of systemic amyloidosis. As recently as 15 yr ago, the only treatment for this disease was melphalan with prednisone administered orally in repeated cycles over many months. This treatment rarely fully eliminates production of the pathogenic monoclonal immunoglobulin light chain, and its impact on survival is modest.[2,3] A more aggressive approach consisting of melphalan administered in myeloablative doses (140 to 200 mg/m^2) followed by autologous stem cell transplantation began to be used in the mid-1990s. Early experience was encouraging. Complete hematologic responses, defined as the absence of detectable monoclonal light chains, and functional improvements, such as resolution of proteinuria among those with kidney involvement, were observed in a substantial proportion of patients.[4–8]

Understandably, many clinicians expressed trepidation about using such intensive treatment for a disease characterized by organ dysfunction that predisposes to treatment-related toxicities. Indeed, rates of treatment-associated mortality from high-dose chemotherapy and autologous stem cell transplantation are consistently higher among patients with AL amyloidosis than among those with multiple myeloma or other malignancies[9–11]; however, with accumulated experience and modifications to treatment protocols and eligibility criteria, toxicities have become more predictable and preventable, and many referral centers with expertise in amyloidosis have come to view high-dosage melphalan with stem cell transplantation (HDM/SCT) as first-line treatment for select patients.[6,9,12] Some centers are now using tandem transplantation (*i.e.*, performing a second course of HDM/SCT) to convert partial hematologic responses to complete hematologic remissions.[13]

An alternative to HDM/SCT that is receiving considerable attention consists of treatment with oral melphalan (typically 0.22 mg/kg per d) together with dexamethasone administered at a high dosage (typically 40 mg/d) in 4-d cycles each month (Mel/Dex). Early reports of Mel/Dex treatment describe rapid eradication of monoclonal light chain production and rapid reduction in N-terminal brain natriuretic peptide, a marker of amyloidosis-associated cardiac dysfunction.[14,15] The treatment is appealing because it does not require mobilization or collection of stem cells and does not produce prolonged periods of profound cytopenia. Thus, individuals for whom HDM/SCT is considered a

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substantial risk might be suitable candidates for this less intensive approach; however, the requirement for repeated courses of high-dosage dexamethasone with associated fluid retention, hemodynamic alterations, and myopathy, as well as the unclear duration of hematologic responses attained with this regimen, are potential drawbacks.

Until 2007, there were no head-to-head comparisons of HDM/SCT with less intensive alternatives. This changed with the publication of the results of a multicenter, randomized trial comparing HDM/SCT with Mel/Dex.[16] The trial randomly assigned 100 patients with AL amyloidosis at 29 centers in France to HDM/SCT or Mel/Dex. In an intention-to-treat analysis, median survival was 56.9 mo in the Mel/Dex group compared with 22.2 mo in the HDM/SCT group ($P = 0.04$). Among the 65 patients for whom hematologic response could be evaluated, a complete response occurred in 32 and 41% of those treated with Mel/Dex and HDM/SCT, respectively, a difference that was not statistically significant. The study investigators concluded that HDM/SCT is not superior to Mel/Dex.

The trial of HDM/SCT *versus* Mel/Dex is important. The findings raise the question of whether HDM/SCT subjects individuals to increased risk without increased benefit and, not surprising, have elicited strong reactions within the amyloidosis community.[17–21] Conducting a multicenter, randomized, controlled trial of HDM/SCT for this rare disease is a major achievement; however, several issues must be considered when interpreting the findings. Only 37 of the 50 patients who were randomly assigned to HDM/SCT actually underwent the treatment, and, of those, only 73% received melphalan at a dosage of 200 mg/m^2. As has been articulated by the investigators and others, treatment-related mortality in the HDM/SCT group (24%) was substantially higher than that reported in single-center studies from amyloidosis referral centers (4 to 14%).[9,12] The high mortality was likely due to enrollment of patients who had severe organ dysfunction and would not be eligible for HDM/SCT at many referral centers and to the limited experience with HDM/SCT for AL amyloidosis at the study sites. The authors appropriately stated in the concluding paragraph of their article that a randomized trial comparing HDM/SCT with Mel/Dex performed at tertiary referral centers might yield different results from those generated by their trial.

So what is the best initial treatment for AL amyloidosis? If treatment is available at a referral center with substantial experience performing SCT specifically for AL amyloidosis, I believe that this aggressive approach should be offered to patients who meet the center's eligibility criteria. In experienced centers, treatment-related mortality is currently $<5\%$,[22] and responses are durable.[23] For patients ineligible for HDM/SCT, Mel/Dex or other alternatives such as lenalidomide- or bortezomib-based regimens should be considered. Until a randomized trial that directly compares HDM/SCT with Mel/Dex is conducted at centers with expertise in treating patients with AL amyloidosis, it is premature to draw conclusions about the relative utilities of these two approaches as initial treatment.

HOW IMPORTANT IS ATTAINMENT OF A COMPLETE HEMATOLOGIC RESPONSE IN AL AMYLOIDOSIS?

The goal of current treatments for AL amyloidosis is to eradicate the plasma cell clone producing the amyloidogenic protein and thereby prevent ongoing amyloid deposition into tissues. Such a goal not only makes intuitive sense but is also supported by observed associations between attainment of a complete hematologic response and improved patient survival and function of affected organs. Recently identified alternatives to melphalan-based treatment such as lenalidomide (a thalidomide analog) and bortezomib (a proteasome inhibitor), as well as tandem SCT, may allow some individuals with persistence of the plasma cell dyscrasia after initial treatment with HDM/SCT or Mel/Dex to achieve a complete hematologic response.[24–27] As a result, many patients are now offered repeated courses of treatment directed at the clonal plasma cells. Given the substantial toxicities associated with any of these treatments and limited information about relative benefits of partial and complete hematologic responses, decisions about how aggressively to pursue additional treatment in the setting of a partial hematologic response can be difficult.

The development of a nephelometric immunoassay for measuring the serum concentration of free light chains may en-

Table 1. Targets of treatments for systemic amyloidoses[a]

Treatment	Amyloidosis Type	Target
Anti-plasma cell agents	AL	Production of amyloidogenic precursor protein
Anti-inflammatory agents	AA	Production of amyloidogenic precursor protein
Orthotopic liver transplantation	Hereditary TTR, Hereditary fibrinogen	Production of amyloidogenic precursor protein
Diflunisal	Hereditary TTR	Conversion of precursor protein to folding intermediate
Fx-1006A	Hereditary TTR, Senile systemic	Conversion of precursor protein to folding intermediate
Eprodisate	AA	Formation of amyloid fibrils
Iododoxorubicin	All types	Stability of amyloid fibrils
CPHPC	All types	Stability of amyloid fibrils

[a]Amyloidosis is not a Food and Drug Administration–approved indication for any of these treatments. AL, amyloid light chain; AA, amyloid A; TTR, transthyretin; CPHPC, R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid.

able better assessment of the relationship between hematologic response and clinical outcomes.[28] In contrast to multiple myeloma, the plasma cell dyscrasia underlying AL amyloidosis is usually low grade. In active disease, the circulating or excreted monoclonal protein is usually detected by immunofixation electrophoresis but often not by less sensitive serum or urine protein electrophoretic studies. Because immunofixation electrophoresis, unlike protein electrophoresis, is not a quantitative test, its utility in the assessment of response to treatment is limited to characterizing the plasma cell dyscrasia as either eradicated or persistent. Most of the studies demonstrating associations between complete hematologic response and both patient survival and function of affected organs were performed using these two discrete categories of hematologic response.[5,7] Similar analyses are starting to be performed using graded hematologic responses that incorporate changes in the serum concentration of free light chains as measured by the nephelometric assay. Although one study suggested that a partial response is associated with improved survival,[29] anecdotal evidence suggests that in some patients, persistence of any circulating amyloidogenic precursor protein in the blood is associated with disease progression. Large follow-up studies will help to gauge the relative importance of complete and partial hematologic responses and enable more informed decisions about how aggressively to pursue a complete hematologic response.

WHAT ROLE DO THE PRECURSORS TO MATURE AMYLOID DEPOSITS PLAY IN AMYLOIDOSIS-ASSOCIATED KIDNEY DYSFUNCTION?

Accumulating evidence from *in vitro* studies and clinical observations suggests the amyloidogenic precursor proteins, folding intermediates, aggregates, and oligomers have tissue and cellular toxicities that contribute to amyloidosis-associated organ dysfunction independent of mature amyloid fibrils.[15,30–36] Distinguishing between the effects of precursor forms and mature fibrils is important for anticipating the impact of treatments that target different processes involved in amyloidogenesis (Table 1).

The effect of eprodisate on kidney function in patients with AA amyloidosis provides some suggestion that amyloidogenic precursors and amyloid fibrils contribute in different ways to the manifestations of amyloidosis-associated kidney disease. Eprodisate is a small sulfonated molecule with structural similarity to heparan sulfate. The compound was designed to inhibit interactions between AA amyloid fibrils and glycosaminoglycans; such interactions promote amyloid fibril formation and stability in tissue.[37,38] In a recently completed placebo-controlled trial of eprodisate for AA amyloidosis, the drug was found to have a beneficial effect on the rate of deterioration in renal function but no effect on urinary protein excretion.[39] Multiple studies and case reports have demonstrated that in both AL and AA amyloid disease, proteinuria decreases, often rapidly, after treatment.[5,8,40–42]; however, all of these observations were made with treatments that suppress production of amyloidogenic precursor proteins, either by targeting the clonal plasma cells in AL disease or by targeting the underlying inflammatory condition that stimulates serum amyloid A synthesis in AA disease. The unexpected finding that eprodisate, a drug that does not affect serum amyloid A levels, preserved kidney function but had no effect on proteinuria raises the interesting possibility that it is the precursors to mature amyloid fibrils that are responsible for proteinuria in amyloidosis. This interpretation of the findings from the clinical trial of eprodisate requires confirmation with additional laboratory and clinical investigation.

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