Treatment of Immunoglobulin Light Chain (Primary or AL) Amyloidosis

This review of the various available options for the treatment of systemic amyloidosis is designed to help the clinician determine which patients are candidates for stem cell transplantation and which should be treated with conventional chemotherapy.

Amyloidosis results from the misfolding of a protein from the native alpha helical state into a beta-pleated sheet. This equilibrium between a soluble precursor and an insoluble end product (the fibril) can be impacted by destabilizing the amyloid fibril protein, and research is under way to cause fibril dissolution, by interfering with binding of the amyloid P component or via antibodies against the fibril itself,[1] that leads to shrinkage of amyloid tumors.[2] These strategies are in early investigative stages, and the only available therapies in the clinic result in reduction of the precursor light chain protein supply, which leads to synthesis of the amyloid fibril. In virtually every instance, the available effective therapy is cytotoxic chemotherapy directed against the plasma cell, the source of amyloid light chain production.

The Role of Stem Cell Transplantation in the Management of Primary Amyloidosis

At Mayo Clinic, stem cell transplantation is the preferred intervention for patients with systemic
amyloidosis who are eligible to receive this therapy. Twenty-five percent of patients receiving stem cell transplantation have been reported to be 10-year survivors, and for patients who achieve a complete response to treatment, the 10-year survival rate is 53%. Histologic regression of amyloid deposits has been seen when chemotherapy normalizes the serum free light chain, and this is most readily done with high doses of chemotherapy. The major impediment to widespread application of stem cell transplantation is the high treatment-related mortality, which we have recently reported has declined to 7%. Renal and cardiac organ responses are seen. With stem cell transplantation, complete hematologic responses were seen in 39% of patients. Organ responses were seen in 47% of patients. The most important predictor of outcome is stage. Even among patients with stage III amyloidosis (NT-proBNP > 332 pg/mL and troponin T > 0.035 mcg/mL), the median survival was 58 months.

Validation of organ responses following stem cell transplantation has been performed using amyloid P component scans. Patients older than 65 years can receive transplants, and improved quality of life has been demonstrated. Key determinants of outcome following transplantation include excessive fluid accumulation during mobilization and the pretransplant value of the immunoglobulin free light chain. Refinement of patient selection is critical to ensure optimal outcomes. The number of organs involved and the extent of cardiac involvement do predict outcome. Reducing the dose of melphalan before transplantation reduces toxicity but also reduces response rate. A prospective randomized study of 100 patients has been reported showing no survival benefit with stem cell transplantation. A systematic review was subsequently published that also did not demonstrate the efficacy of stem cell transplantation. The high treatment-related mortality reported in these studies is a major concern.

**TABLE**

### Transplantation Eligibility Criteria

Currently at Mayo Clinic, approximately 20% of patients with amyloidosis are eligible for stem cell transplantation. Advanced cardiac involvement and renal insufficiency are both contraindications to high-dose therapy before transplantation. It is clear from these studies that transplantation in high-risk patients should not be undertaken, but an important question is still whether a more carefully selected cohort benefits from stem cell transplantation; we believe that the answer is yes, pending further trials. (The table outlines the transplantation eligibility criteria applied in patient selection at Mayo Clinic.)

### Melphalan-Based Chemotherapy

The melphalan-prednisone combination has been shown to be superior to treatment with colchicine alone. Continuous oral low-dose melphalan provides palliation, although the response rates are low. In a seminal paper with 5 years of follow-up, outcomes in 46 patients ineligible for stem cell transplantation were reported, with organ responses in 48%, a 6-year actuarial survival rate of 50%, and a progression-free survival rate of 40%; the median overall survival time was 5.1 years. This regimen is widely considered to be the standard of therapy for patients who are not eligible for stem cell transplantation. Others have reported far poorer results. A cohort of patients treated with oral melphalan and dexamethasone had a median survival time of only 10.5 months. A second report using parenteral melphalan with dexamethasone in 61 patients reported a median survival of 17.5 months and a 3-month all-cause mortality of 28%.

Much of the variability in outcomes is related to the proportion of patients with advanced cardiac amyloidosis who are included. Of 48 evaluable patients treated at Boston University with melphalan and dexamethasone, a complete hematologic response was achieved in 13% and a partial hematologic response was observed in 25%. Median survival for all 70 patients has not been reached, with a median follow-up of 17 months. The widely disparate survivals reported from these four studies reflect the heterogeneity of amyloidosis and the importance of recognizing the proportion of patients enrolled with advanced cardiac involvement.
Guidelines for treatment of newly diagnosed primary amyloidosis. Information from Reference 49.

At Mayo Clinic, treatment with melphalan and dexamethasone is still considered a standard for nonstudy, nontransplant intervention (Figure 2). Because this combination has a relatively low toxicity profile, it can produce hematologic responses, and its oral availability makes it easy to tolerate. Because of the survival benefit seen with the use of novel agents when combined with traditional chemotherapy in patients with myeloma, novel agents have been rapidly adapted to the armamentarium of treatment of systemic amyloidosis.

**Thalidomide**

Two series that used thalidomide (Thalomid) as a single agent with steroids have been published. In one, 16 patients were enrolled.[24] The maximum tolerated dose was 300 mg. Thalidomide tolerance in patients with light chain amyloid-osis was inferior to that seen in patients with multiple myeloma, with grade III-IV toxicity in half of the amyloidosis patients; 25% had to discontinue therapy. In a second report of thalidomide use in 12 patients with amyloidosis, edema, cognitive difficulties, and constipation were seen in 9; dyspnea, dizziness, and rash in 6; and renal insufficiency in 5 patients.[25] The median time on therapy was only 72 days. In a study in Italy, 31 patients received thalidomide starting at a dosage of 100 mg/d, escalating up to 400 mg/d, combined with 4-day pulses of dexamethasone.[26] A hematologic response was seen in 48%, with 26% having organ responses. The median time to response was 3.6 months. Thalidomide was active, but the toxicity was substantial. Thus, the initial dose of thalidomide should not exceed 100 mg/d, and in the elderly, the initial dose should not exceed 50 mg/d. Thalidomide has also been combined with melphalan and dexamethasone.[27] In 22 patients with advanced cardiac amyloidosis, 8 hematologic responses and 4 organ responses were reported, but 6 patients died of advanced disease before completing cycle 3. Early treatment death is a common clinical trial outcome in patients with cardiac amyloidosis. Cyclophosphamide has been combined with thalidomide and dexamethasone in a risk-adapted fashion.[28] Seventy-five patients with advanced amyloidosis were treated. The full dose given to 51 patients consisted of a 21-day cycle of oral cyclophosphamide, at 500 mg once weekly; thalidomide, at 200 mg/d continuously; and dexamethasone, at 40 mg on days 1 to 4 and 9 to 12. In patients older than 70 years, those with heart failure, and those with considerable fluid overload (n = 24), the attenuated regimen consisted of a 28-day cycle of cyclophosphamide, at 500 mg on days 1, 8, and 15; thalidomide, at 200 mg/d; and dexamethasone, at 20 mg on days 1 to 4 and 15 to 18. A hematologic response was seen in 74% of 65 evaluable patients, with complete responses in 21%. Median overall survival from the start of therapy was 41 months. Toxicity necessitating cessation of therapy occurred in 8% and was grade 2 in 52%. Treatment-related mortality was only 4%. In an abstract presented in 2010 at the annual meeting of the American Society of Hematology,[29] organ responses appeared to be significantly better with a cyclophosphamide-thalidomide-dexamethasone combination compared with melphalan-dexamethasone, possibly due to more rapid response to the cyclophosphamide-thalidomide-dexamethasone regimen. However, this higher organ response rate did not translate into a survival advantage. The depth of clonal response was directly related to improvement in survival.

**Lenalidomide**

Lenalidomide (Revlimid) has been combined with dexamethasone in the treatment of primary amyloidosis.[30] In the first phase II trial, 34 patients received 25 mg/d, which was poorly tolerated and was reduced to 15 mg/d. Of 24 evaluable patients, 29% achieved a hematologic complete
response, and 38% achieved a partial hematologic response, for an overall hematologic response rate of 67%.

In a follow-up study, a total of 69 patients treated with lenalidomide and dexamethasone were accrued.\[31\] Lenalidomide, alone and in combination with dexamethasone, induced hematologic complete responses in 16% of previously treated patients with primary amyloidosis. Most complete responses occurred within 6 months after treatment was initiated, and 60% of complete responses were durable, even off treatment. The median progression-free survival time of patients while on the study was 49.8 months.

In a second trial including 23 patients, lenalidomide was given first alone, and dexamethasone was added if a response was not seen after 3 cycles.\[32\] Within the first 3 cycles of therapy, treatment was discontinued in 10 patients because of progression, death, or intolerance of therapy. Of 10 responses, 9 required dexamethasone. Adverse effects included cytopenia, rash, and fatigue. At a median follow-up of 33.6 months, 22 patients had died. The median response duration and survival time were 19.2 and 31 months, respectively.

Lenalidomide has also been combined with melphalan and dexamethasone.\[33\] The maximum tolerated dose of lenalidomide was 15 mg (for 21 days every 28 days) combined with standard melphalan and dexamethasone. Hematologic and organ responses were seen in 60% and 50% of patients, respectively. A phase III trial comparing a melphalan-dexamethasone combination with melphalan-dexamethasone-lenalidomide is planned.

Lenalidomide was combined with low-dose dexamethasone and cyclophosphamide in a phase I-II study.\[34\] Patients received 20 mg of dexamethasone for 4 days, cyclophosphamide at 100 mg/d for 10 days, and lenalidomide at 15 mg, for 21 of 28 days. The response rate for evaluable patients was 64%. The median time to response was 2.5 months. Organ responses were seen in five patients. An Italian trial of a cyclophosphamide-lenalidomide-dexamethasone combination studied 20 patients.\[35\] Four patients died at a median of 8 months because of heart failure. Eight patients achieved a hematologic response, which was complete in one patient. Organ response was reached in three patients. Using the same regimen at Mayo Clinic, the overall hematologic response rate was 60% (21 patients; complete response in 2, very good partial response in 10, and partial response in 9), and hematologic responses were observed in 79% of stage I and II patients and 40% of stage III patients.\[36\] Among patients receiving at least 4 cycles of therapy, the response rate was 87% (20 of 23) — with complete response in 2, very good partial response in 10, and partial response in 8 patients.

Evaluating organ responses in lenalidomide-treated patients can be challenging because there appears to be discordance between cardiac biomarkers and a free light chain response in patients with amyloidosis.\[37\] Type B natriuretic peptide (BNP) increased by more than 30% in a substantial proportion of patients with primary amyloidosis during treatment with lenalidomide. In patients with primary amyloidosis whose BNP rises while receiving lenalidomide, the assumption should not be made that the treatment is failing without other signs of disease progression. The increase in BNP after initiation of lenalidomide therapy raises a question as to whether lenalidomide-based therapy increases cardiac toxicity or whether the cardiac biomarkers are not a valid measure of response in lenalidomide-treated amyloidosis patients.\[38\] Among patients with primary amyloidosis, worsening of kidney function occurs frequently during lenalidomide therapy, and kidney function needs to be carefully monitored during therapy.\[39\] Durable hematologic complete responses can be achieved with lenalidomide.

**Pomalidomide**

Pomalidomide (CC-4047, Actimid), a derivative of thalidomide with structural similarity to both thalidomide and lenalidomide, was administered to 29 evaluable patients who were all previously treated; 24 had cardiac involvement.\[40\] Neutropenia was seen in 10 and fatigue in 4. One patient died from cardiac amyloidosis 4 days after initiating therapy. At a median time on study of 8.4 months, 18 patients had discontinued therapy. The overall hematologic response rate in the heavily pretreated population was 38%, with eight partial responses and three very good partial responses, including six responses among 14 patients in whom prior lenalidomide or thalidomide therapy had failed. Three organ responses have been confirmed thus far. The 1-year progression-free survival and overall survival rates were 56% and 77%, respectively. Pomalidomide and dexamethasone showed activity in heavily pretreated amyloidosis.

**Bortezomib**
Bortezomib (Velcade) has the ability to inhibit the proteosome. This can result in a load for the endoplasmic reticulum that can lead to rapid cellular death.[41] In an initial report, 18 patients were treated with bortezomib and dexamethasone; 61% had two or more organs involved; and 15 had cardiac involvement.[42] A hematologic response was seen in 94%, and 44% had a complete hematologic response. Neurotoxicity, fatigue, edema, constipation, and postural hypotension were serious adverse effects in patients on the twice-weekly schedule.

<table>
<thead>
<tr>
<th>Reference Guide</th>
</tr>
</thead>
</table>

Bortezomib was administered to 20 patients with amyloidosis who had received a median of three prior regimens of chemotherapy before enrollment in the bortezomib trial.[43] Forty-five percent received dexamethasone. Fifteen percent achieved a complete hematologic response, and 65% had a partial hematologic response. Toxicity was seen in 75% of patients and required discontinuation of therapy in 40% of patients.

In a phase I–II dose-escalation study, bortezomib was given in both weekly and twice-weekly schedules.[44] Thirty-one patients were enrolled across seven cohorts. No corticosteroids were given. Patients with New York Heart Association class III heart failure were excluded from this study, so the value of the agent in advanced cardiac amyloidosis is unclear. Hematologic responses were
seen in 50% of patients, including 20% complete responses; median time to response was 1.2 months. There has been a shift from twice-weekly to once-weekly bortezomib therapy to reduce the toxic effects in these fragile patients. Amyloidosis relapsing after autologous stem cell transplantation has been treated with bortezomib; this has resulted in normalization of free light chains and has the potential to render patients previously ineligible for transplant safe to receive high-dose therapy.[45]

A multicenter survey of bortezomib, with or without dexamethasone, was performed at three amyloidosis treatment centers.[46] Hematologic responses were seen in 71%, with 25% complete responses. In previously untreated patients, the complete response was 47%, the 1-year survival was 76%, and the NT-proBNP was independently associated with survival. Toxic effects included neuropathy, orthostatic hypotension, edema, constipation, and diarrhea. Bortezomib with or without dexamethasone was active in primary amyloidosis and produced rapid responses and higher rates of hematologic and organ responses.

An Austrian group reported a retrospective evaluation of bortezomib and dexamethasone in 26 patients with primary amyloidosis, 18 of whom received the combination as first-line therapy.[47] All had renal involvement, and 35% had cardiac involvement. The overall response rate was 54%. Organ functional improvement was seen in 12%. The median progression-free and overall survival times were 5 and 18.7 months, respectively.

A European collaborative study included 428 patients with primary amyloidosis; 204 received melphalan-dexamethasone, 155 received cyclophosphamide-thalidomide-dexamethasone, 28 received bortezomib-dexamethasone, 25 received cyclophosphamide-lenalidomide-dexamethasone, and 13 received autologous stem cell transplantation.[29] There was a significantly greater reduction in the difference between the involved and uninvolved free light chain levels after bortezomib-dexamethasone (median reduction, 91%). Studies trying to confirm the benefits of bortezomib combination chemotherapy are under way in the United States and Europe, randomizing patients between treatment arms with a melphalan-dexamethasone combination and a melphalan-dexamethasone-bortezomib combination (Clinicaltrials.gov identifier NCT01078454).

**Carfilzomib**

Carfilzomib (PR-171) is an irreversible proteasome inhibitor that appears to lack neurotoxicity and has been combined with lenalidomide and dexamethasone in the treatment of newly diagnosed multiple myeloma as well as in relapsed multiple myeloma.[48] Baseline peripheral neuropathy does not have an impact on the efficacy of this agent, and a trial to use carfilzomib in combination with dexamethasone in the treatment of patients with amyloidosis has been proposed.

**Conclusion**

Guidelines for the therapy of previously treated primary amyloidosis. Information from Reference 49.

The optimal therapy for primary amyloidosis remains unknown. Virtually all patients today receive some form of cytotoxic chemotherapy. Stem cell transplantation is widely used but only 20% of patients are appropriate candidates for transplantation. When primary amyloidosis is diagnosed before the development of advanced cardiomyopathy, hematologic and organ responses are achievable with a wide array of chemotherapy protocols. The combination of melphalan and dexamethasone appears to be the established standard of care for patients with amyloidosis, but results are highly variable. Bortezomib seems to have a high level of activity in achieving responses, but longer follow-up is required to determine the durability of response and the overall impact on survival. Recommendations for treatment of newly diagnosed and relapsed primary amyloidosis are shown in Figures 2 and 3.

**Financial Disclosure: Dr. Gertz has received project support from Celgene, Millennium, Neotope,**
Eisai Inc., Lilly Research Laboratories, OptumHealth Education, Research To Practice, Physicians’ Education Resource, and Amgen Inc.

References:


32. Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without


