

Primary Systemic Amyloidosis

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Current Treatment Options in Oncology 2000, 1:83-89
Current Science, Inc. ISSN 1527-2729
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Opinion Statement

Patients with unexplained heart failure, hepatomegaly, nephrotic syndrome, or peripheral neuropathy should be evaluated for primary systemic (amyloid light-chain, or AL) amyloidosis by first seeking evidence of a clonal plasma cell disorder with serum and urine immunofixation studies, as well as a bone marrow biopsy. Immunostaining of the marrow biopsy for lambda and kappa isotypes will usually demonstrate a dominant clonal population of plasma cells if immunofixation studies are negative (less than 10% of cases). Tissue diagnosis of amyloidosis should be sought by biopsy of the abdominal fat or an involved organ. In addition, patients with stable myeloma or monoclonal gammopathy of undetermined significance who develop such conditions or become progressively ill should be evaluated for amyloidosis. We recommend that newly diagnosed patients with AL amyloidosis, who meet criteria for autologous hematopoietic cell transplantation, be considered for high-dose melphalan with stem cell support. Criteria usually include adequate cardiac, pulmonary, and hepatic function. AL amyloidosis patients treated with autologous transplantation frequently achieve durable complete remissions of the plasma cell disease and marked improvement in amyloid-related organ dysfunction. AL amyloidosis patients with dominant cardiac amyloid, who are without symptomatic pleural effusions and have no history of cardiac syncope or symptomatic arrhythmias, may be considered for autologous transplantation but are at increased risk of peritransplant mortality. Autologous transplantation should not routinely be offered to patients with dominant cardiac amyloid with recurrent effusions or histories of syncope or arrhythmias or to patients older than 50 years of age with more than two major organ systems involved (eg, heart, kidneys, liver, and peripheral nerves). We recommend that AL patients with isolated advanced cardiac or hepatic amyloidosis be considered for solid organ replacement followed by autologous transplantation. Otherwise, AL patients who are elderly or ineligible for autologous transplantation may be treated with oral melphalan (Alkeran, GlaxoWellcome, Middlesex, UK) and prednisone; however, because the response rate is only about 25% and the prognosis poor, such patients might also be enrolled on clinical trials of emerging therapies.

Introduction

Primary systemic or AL amyloidosis is the most common cause of amyloidosis in the Western world, but remains a rare disorder with an estimated annual incidence of about 3000 cases in the United States [1**]. AL amyloidosis is a disease with two distinctive features. First, AL amyloidosis is a disease of clonal plasma cells similar to multiple myeloma and to monoclonal gammopathy of undetermined significance. Second, AL is a disease of abnormal protein deposits in organs such as the heart, kidneys, lungs, liver, spleen, gastrointestinal tract, skin, joints, lymph nodes, and peripheral nervous system [2*, 3*,4, 5]. Criteria for defining amyloid-related organ involvement are provided in [Table 1](#).

Table 1: Clinical and noninvasive criteria for determining amyloid-related major organ involvement*

Heart

Echocardiogram showing increased ventricular wall thickness and thickened valves with no history of hypertension or valvular heart disease

Electrocardiogram showing unexplained low voltage

NYHA Class 2 or higher without ischemic heart disease

Kidneys

24-hour proteinuria greater than 500 mg

Liver

RUQ discomfort

Early satiety

Hepatomegaly

Increased alkaline phosphatase

Increased C-reactive protein

Peripheral nervous system

Orthostatic hypotension

Lower extremity sensory or polyneuropathy

Chronic nausea, dysgeusia, early satiety

Impotence, diarrhea, or constipation

*In all instances, a positive tissue biopsy remains the gold standard. NYHA--New York Heart Association; RUQ--right upper quadrant.

The plasma cells in AL amyloidosis are clonal and demonstrate clonality by secreting the same antibody or monoclonal protein. Usually these monoclonal proteins contain both heavy and light chains as normal antibodies do, or are comprised of one of the two types of light chains (kappa or lambda) without associated heavy chains. The deposited protein is amyloid, an unusual mix of fibrils composed of monoclonal light chains and an assortment of other normal proteins. Amyloidosis occurs because the monoclonal antibody or light chain produced by the patient's clonal plasma cells has abnormal physical properties. Monoclonal light chains from patients with AL can be purified and induced to form synthetic amyloid in test tubes. All AL amyloid deposits have been shown to be intact light chains or fragments of light or heavy chains. Lambda light chains occur more frequently in AL than kappa (lambda-kappa ratio 4:1).

Amyloid can be identified if a tissue biopsy is stained with specific chemicals, such as the dye Congo red. Amyloid in tissue stained with Congo red possesses a unique property as it changes from orange-pink to apple-green when viewed microscopically using polarized light. Amyloid also has a distinctive morphology or structure when viewed with an electron microscope; it forms linear nonbranching fibrils with a width of approximately 9.5 nanometers. Why some monoclonal proteins form amyloid and others do not has not yet been determined [6]. Amyloid light chain fibrils are comprised mostly of monoclonal light chains organized in extracellular deposits that resist proteolysis and are frequently described as amorphous or hyaline deposits.

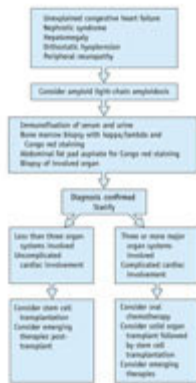


Figure 1

An approach to diagnosis and treatment of amyloid light-chain amyloidosis.

[View larger image](#)

Because these deposits in key viscera, such as the heart or liver, may progress rapidly, AL can be an acutely fatal disease with death occurring soon after diagnosis, although most patients do not succumb quite so quickly. Newly diagnosed patients treated with oral melphalan and prednisone have a median survival of 18 months, a modest but significant improvement in comparison to controls with a median survival of about 12 months [7*, 8]. Complete elimination of the clonal plasma cell disease and improvements in amyloid-related organ dysfunction are not observed with any frequency in patients treated with oral melphalan and prednisone. Neither dexamethasone nor combination chemotherapy significantly improve such outcomes or prolong survival [9, 10]. However, with high-dose melphalan and autologous stem-cell transplantation, durable complete responses of the plasma cell disorder, improvements of amyloid-related organ disease, and prolonged survival have frequently been observed [11**, 12**, 13, 14, 15*].

The treatment of AL amyloidosis then involves the same chemotherapeutic agents used to treat multiple myeloma. The goal is to reduce or stop the production of monoclonal light chains by reducing or eliminating clonal plasma cells. Autologous transplantation can provide effective treatment of AL amyloidosis for select patients. Amyloid deposits in the marrow do not interfere with stem-cell mobilization or engraftment. Once the process of active deposition is halted, amyloid deposits are slowly resorbed by the body. Supportive care considerations in AL amyloidosis involve the use of a variety of measures and agents designed to palliate symptoms associated with malfunctioning organs [16**]. An approach to diagnosing and treating patients with AL is provided in [Figure 1](#).

Treatment

Diet and lifestyle

- Patients with kidney, and especially heart and kidney, involvement should follow a salt-restricted diet. Excess salt intake can worsen peripheral edema and pleural effusions.
- The only caveat in relation to salt restriction applies to patients with severe orthostatic hypotension. Orthostatic symptoms may worsen with diminished salt intake.
- Patients with kidney involvement should avoid medications that can worsen renal function, particularly nonsteroidal anti-inflammatory drugs.
- Patients experiencing early satiety due to hepatic amyloid or decreased gastric

tone, as well as patients recovering from stem cell transplant, may increase their nutrient intake with multiple small meals (grazing) as opposed to eating three meals a day.

- Mechanical maneuvers such as the use of compressive stockings to minimize lower extremity edema or leg elevation during sitting may help significantly in patients with nephrotic syndrome and low serum albumin levels.
- Dehydration must be avoided.

Pharmacologic treatment

- Because of the limited visceral reserve patients with AL amyloidosis possess, the risks of polypharmacy, particularly in the setting of stem-cell transplantation, cannot be overemphasized.
- The most useful clinical tools for the assessment of volume status in patients with AL amyloidosis are orthostatic vital signs properly obtained and examination of the neck veins, heart, and lungs. The presence of lower extremity edema can be a deceptive indicator of volume status. The use of diuretic therapy should be regulated by orthostatic signs and exam findings. The risk of over-diuresis may be greater than the risk of some peripheral edema in the setting of clinical euvolemia.
- Patients with AL amyloidosis with cardiac involvement who are taking corticosteroids should have their potassium levels monitored regularly to minimize the risk of hypokalemic arrhythmias.
- Amyloid light chain amyloidosis patients with symptomatic ventricular or atrial arrhythmias can be effectively treated with amiodarone. Automated implantable cardiac defibrillator/pacers are of limited value, even in patients who have inducible arrhythmias.
- Medications such as calcium-channel blockers or β -blockers may be particularly difficult for patients with AL to tolerate and usually should be discontinued or avoided.
- Ten percent of AL patients are hypothyroid. The symptoms of AL may mask symptomatic hypothyroidism. The thyroid-stimulating hormone level should be checked at diagnosis and hormone supplementation provided as indicated.
- In patients with renal involvement and normal creatinine levels, anemia may occur because erythropoietin levels are inappropriately low. Erythropoietin levels should be checked and supplementation given if indicated.

- In patients with renal involvement, renal vein thrombosis may account for rapid deterioration of function and can be diagnosed by magnetic resonance imaging or renal scan.
- Adrenal insufficiency occurs about 10% of the time in patients with advanced renal amyloid. Appropriate tests should be employed to evaluate this diagnosis.
- For men with AL and impotence, sildenafil citrate (Viagra, Pfizer, New York, NY) is often effective.
- For patients with delayed gastric emptying documented by gastric emptying scan, gastric motility agents, such as cisapride, are often effective.
- Stem-cell mobilization can be achieved with granulocyte colony-stimulating factor (G-CSF) or G-CSF combined with granulocyte-macrophage colony-stimulating factor (GM-CSF). Patients should be followed for development of hypotension, hypoxia, or pulmonary edema during stem-cell mobilization. Growth-factor administration and stem-cell collection should be discontinued in patients who experience such side effects.

Prednisone

Standard dosage Prednisone has been prescribed with Alkeran (GlaxoWellcome, Research Triangle Park, NC) to treat AL and myeloma patients for many years at doses of 100 mg/d for 4 days or 60 mg/d for 7 days. Usually given for 10 to 12 months or to maximum response of the M protein as measured in serum or urine.

Contraindications Relative contraindications include diabetes mellitus, congestive heart failure, and gastrointestinal (GI) bleeding.

Main drug interactions Innumerable.

Main side effects Hypokalemia, increased serum glucose, fluid retention.

Special points Should be taken with meals or on a full stomach and used with gastrointestinal (GI) prophylaxis.

Cost effectiveness The cost of 10 mg of prednisone is \$0.10.

Alkeran (oral melphalan)

Standard dosage Alkeran for oral use is available in 2 mg tablets. For 4 day regimens the standard dose is 0.25 mg/kg/d. For 7 day regimens the dose is usually 0.15 mg/kg/d. Usually given for 10 to 12 months or to maximum response of the M protein.

Contraindications Neutropenia, thrombocytopenia, prior adverse reactions, myelodysplasia.

Main drug Food may decrease absorption.

interactions

Main side effects Depressed blood cell counts, neutropenic fever, secondary leukemia.

Special points Should be taken on an empty stomach at least 30 minutes before a meal.

Cost effectiveness Inexpensive.

Dexamethasone

Standard dosage Forty mg/d, or 20 mg/m²/d in petite individuals, for 4 days. Often given in 28 day cycles as follows: on days 1 through 4, 9 through 13, and 17 through 20. May be given intravenously daily for 4 days every 21 days. Usually given for 2 to 4 cycles.

Contraindications Systemic fungal infections, active gastritis, or ulcer disease.

Main drug interactions Ephedrine.

Main side effects GI bleeding. Central nervous system symptoms may include a hypermanic state and insomnia.

Special points GI and antifungal prophylaxis are indicated.

Cost effectiveness Relatively inexpensive.

Intravenous melphalan

Standard dosage Doses range from 70 mg/m² to 200 mg/m². For patients on dialysis or over 61 years of age, it is recommended that 100 mg/m² or 140 mg/m² be used with blood stem-cell support. Usually given in two divided doses daily for 2 days.

Contraindications Active infections, active gastrointestinal bleeding.

Main drug interactions Few.

Main side effects Alopecia, depressed blood counts, stomatitis, and mucositis.

Special points Must be used within an established stem-cell transplantation unit and only after prior collection of blood stem cells. Stem cell support should contain a minimum of 2 x 10⁶ CD34+ cells per kg. May cause delayed emesis for up to 7 days.

Cost effectiveness Inexpensive even for high-dose therapy.

Supportive care

- During routine hospitalization, it is important to minimize the use of intravenous saline unless its use is clearly indicated. Patients with AL are unusually salt avid and tend to retain salt and become edematous with minimal infusions. Intravascular volume can be maintained and enhanced with intravenous salt-poor albumin to maintain a serum albumin level greater than 2 g/dL. Such an approach can also enhance the efficacy of diuretics.

- Loop diuretics combined with spironolactone are often effective in maintaining patients at their dry weight. For more aggressive diuresis, metolazone can be added every third day or, in the hospital, renal dose dopamine can be used for extended periods.
- Management of volume status is a critical aspect of stem cell transplantation in patients with AL. Maintenance of clinical euvolemia requires vigilance, diligence, and twice-daily clinical assessments as described previously. The risk of overdiuresis during the time of neutropenia and G-CSF administration cannot be overemphasized.
- Gastrointestinal tract involvement with AL can be focal or diffuse, and symptoms usually are linked to the location and extent of AL deposits. The entire length of the gastrointestinal tract may be involved; macroglossia, which occurs in about 10% of patients, can be massive and can produce the inability to eat or drink normally, as well as airway obstruction and sleep apnea. Achalasia, hematemesis, gastroparesis, and pseudo-obstruction are among the many possible manifestations of gastrointestinal amyloid. Therefore, planning prior to stem cell transplantation is essential. Evaluation should include a detailed review of gastrointestinal signs and symptoms, serial stool guaiacs, endoscopic studies to define pathology when indicated by symptoms or other findings, and a complete assessment of coagulation status. If amyloid extensively infiltrates the submucosa of the stomach or lower tract, the potential for severe mucositis with hemorrhage must be anticipated. Neuropathic compromise of the enteric plexus often results in atony, persistent post-transplant nausea and failure to thrive. Prior to transplant, a plan should be developed for the management of GI amyloid, if present, with respect to extended antiemetic regimens, prophylaxis and management of GI bleeding, and re-feeding.
- Regular stool guaiacs are important tools in the management of patients with AL, no matter what therapy is used. Standard evaluations should follow identification of evidence for occult gastrointestinal blood loss. Proton-pump inhibitors are particularly useful for AL patients with upper GI oozing due to diffuse amyloid infiltration.
- Major GI bleeds can present atypically as new onset atrial fibrillation or supraventricular tachycardia, or more typically as hemodynamic instability. In patients with known GI amyloid, if stool guaiacs are positive during stem cell transplantation, the hematocrit should be maintained at more than 30% and platelets at more than 50,000/ μ L. In addition, visceral perforation or rupture due to amyloid can occur (although rare) in the peritransplant period. Vague or atypical left-sided abdominal or shoulder pain should raise concern about occult splenic hemorrhage and lead to consideration of imaging the abdomen. Splenic rupture in this period has occurred and must be managed surgically; patients can survive. Other viscera, such as the esophagus or bowel, can also perforate and present life-threatening challenges.
- Midodrine and fludrocortisone are useful agents to treat orthostasis but do not work reliably in the transplant setting. Careful management of volume status will help avoid many of the pitfalls associated with hypotension. Other valuable supportive care measures in the transplant setting include use of incentive

spirometry, nutritional and protein supplements, and daily psychiatric visits.

- In patients with renal involvement and normal creatinine levels, anemia may occur because erythropoietin (EPO) levels are inappropriately low. EPO levels should be checked and supplementation given if indicated.
- Renal transplantation has been performed in a limited number of patients with AL on dialysis, with surprisingly good long-term survival rates.

Emerging therapies

- Iodinated doxorubicin is the first agent that may help to dissolve amyloid deposits in select patients; it is currently in clinical trials [17].
- Enbrel (Etanercept, Immunex, Seattle, WA), an agent that competitively inhibits the binding of tumor necrosis factor (TNF) molecules to the TNF receptor, is also currently in clinical trials.
- Thalidomide, a drug recently shown to be effective in refractory myeloma, is currently being used in clinical trials in AL as well.

References and Recommended Reading

Recently published papers of particular interest have been highlighted as:

- * Of importance
- ** Of major importance

- 1.** Gertz MA: **Amyloidosis: recognition, confirmation, prognosis, and therapy.** *Mayo Clin Proc* 1999, **74**:490-494.

**

This is a concise review designed to alert the primary care physician to the signs and symptoms of amyloid light-chain amyloidosis.

► View the [PubMed notation](#) for this reference.

- 2.** Gillmore JD: **Amyloidosis: a review of recent diagnostic and therapeutic developments.** *Br J Haematol* 1997, **99**:245-258.

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In this review, a comprehensive therapeutic algorithm is offered to guide decisions

regarding the treatment of AL patients.

▶ View the [PubMed notation](#) for this reference.

3. Falk RH: The systemic amyloidoses: current approaches to diagnosis and treatment. *N Engl J Med* 1997, **337:898-910.**

In this review, a broad account of the various forms of amyloidosis and their presentation is offered with helpful diagnostic guidelines.

▶ View the [PubMed notation](#) for this reference.

4. Gertz MA: Hepatic amyloidosis: clinical appraisal in 77 patients. *Hepatology* 1997, **25:118-121.**

▶ View the [PubMed notation](#) for this reference.

5. Rajkumar SV: Prognosis of patients with primary systemic amyloidosis who present with dominant neuropathy. *Am J Med* 1998, **104:232-237.**

▶ View the [PubMed notation](#) for this reference.

6. Schormann N: Tertiary structure of an amyloid immunoglobulin light chain protein: a proposed model for amyloid fibril formation. *Proc Natl Acad Sci USA* 1995, **92:9490-9500.**

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7. Kyle R, et al.: A trial of three regimes for primary amyloidosis: colchicine alone, melphalan and prednisolone, and melphalan, prednisolone and colchicine. *N Engl J Med* 1997, **336:1202-1207.**

This is one of the largest clinical trials ever conducted in AL amyloidosis and confirms a role for cytoreductive therapies.

► View the [PubMed notation](#) for this reference.

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8. Skinner M, *et al.*: **Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine alone.** *Am J Med* 1996, **100**:290-298.

► View the [PubMed notation](#) for this reference.

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9. Gertz MA, *et al.*: **Phase II trial of high-dose dexamethasone for untreated patients with primary systemic amyloidosis.** *Med Oncol* 1999, **16**:104-109.

► View the [PubMed notation](#) for this reference.

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10. Gertz MA, *et al.*: **Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis.** *J Clin Oncol* 1999, **17**:262-267.

► View the [PubMed notation](#) for this reference.

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11. ****** Comenzo RL, *et al.*: **Dose- intensive melphalan with blood stem-cell support for the treatment of AL amyloidosis: survival and responses in 25 patients.** *Blood* 1998, **91**:3662-3670.

This is the report of a phase II trial using stem cell transplant to treat 25 patients with AL. The benefits of stem cell transplant are well described with respect to the reversal of AL organ involvement.

► View the [PubMed notation](#) for this reference.

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12. ****** Comenzo RL, *et al.*: **Intermediate-dose intravenous melphalan and blood stem cells mobilized with sequential GM+G-CFS or G-CSF alone to treat AL (amyloid light chain) amyloidosis.** *Br J*

Haematol 1999, **104**:553-564.

In this report of a phase II trial, AL patients received lower doses of intravenous melphalan with stem cells in an attempt to extend the benefits of intravenous melphalan to older and sicker patients. Although some patients benefitted, the transplant-related 100 day mortality remained 20%, and the need for better patient selection is discussed.

► View the [PubMed notation](#) for this reference.

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- 13.** Patriarca F, *et al.*: **Improvement of amyloid-related symptoms after autologous stem cell transplantation in a patient with hepatomegaly, macroglossia and purpura.** *Bone Marrow Transplant* 1999, **24**:433-435.

► View the [PubMed notation](#) for this reference.

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- 14.** Sezer O, *et al.*: **Rapid reversal of nephrotic syndrome due to primary systemic AL amyloidosis after VAD and subsequent high-dose chemotherapy with autologous stem cell support.** *Bone Marrow Transplant* 1999, **23**:967-969.

► View the [PubMed notation](#) for this reference.

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- 15.** Comenzo RL: **Hematopoietic transplantation for primary systemic amyloidosis: what have we learned?** *Leuk Lymphoma*. In p.

This review provides an overview of the initial 4 years of stem cell transplant for AL with an emphasis on prognostic factors and the risks of stem cell transplant.

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- 16.** Merlini G.: **Treatment of primary amyloidosis.** *Semin Hematol* 1995, **32**:60-79.

This is an excellent review of supportive care measures that are important for managing the many symptoms of systemic amyloidosis.

► View the [PubMed notation](#) for this reference.

17. Merlini G, *et al.*: **Treatment of AL amyloidosis with 4'-Iodo-4'-deoxydoxorubicin: an update [letter]**. *Blood* 1999, **93**:1112-1113.

▶ View the [PubMed notation](#) for this reference.
