Primary Systemic Amyloidosis

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Opinion statement

Primary amyloidosis is a plasma cell dyscrasia in which insoluble immunoglobulin light chain fragments are produced and polymerize into fibrils that deposit extracellularly, causing visceral organ dysfunction and death. The disorder is rare. Its recognition requires understanding the association between nephrotic syndrome, cardiomyopathy, peripheral neuropathy, and hepatomegaly with amyloidosis. The most important screening test for amyloidosis is immunofixation of the serum and urine to detect a monoclonal immunoglobulin light chain. All patients need the diagnosis confirmed histologically. The least invasive source of tissue for amyloid detection is the subcutaneous fat. The most important prognostic factor is whether there is cardiac involvement, which is best assessed by echocardiography with Doppler studies. Therapies used include oral melphalan/prednisone and high-dose corticosteroids. High-dose chemotherapy followed by stem cell reconstitution seems to provide the highest reported response rates. Transplant is associated with unique morbidities not seen in the transplantation of patients with other hematologic malignancies.

Introduction

Amyloidosis has been classified histologically as any extracellular deposit that binds Congo red. These deposits must demonstrate green birefringence when viewed under polarized light. Under the electron microscope, amyloid deposits are rigid, nonbranching fibrils of indefinite length and a width of 9.5 nm. In the early part of the 20th century, the ultrastructure of amyloid and its amino acid sequence were not understood; therefore, the disease was classified on the basis of its anatomic distribution. During the first half of the 20th century, three types of amyloidosis were recognized. Amyloidosis seen with an autosomal-dominant inheritance pattern was classified as familial (AF) [1]. Amyloidosis seen in the presence of long-standing infections, such as tuberculosis or osteomyelitis, or alternatively with long-standing symmetric polyarthritis or inflammatory bowel disease was classified as secondary (AA) [2]. Virtually all other forms of amyloidosis seen were designated as primary (AL). Any amyloidosis that was idiopathic in origin was considered primary. Currently, amyloidosis is classified by the subunit protein comprising the amyloid fibril. Table 1 provides an abridged nomenclature for amyloidosis. Of all the forms of amyloid, only AL is composed of immunoglobulin light chains and is associated with a plasma cell dyscrasia.

It is possible to produce synthetic fibrils of AL in vitro from purified human Bence Jones proteins (immunoglobulin light chains). All known forms of AL are composed from the N-terminal fragment of an immunoglobulin light chain or heavy chain (AH) [3•]. It is presumed that the amino acid structure of immunoglobulin light chains is unique in patients who develop amyloidosis. Immunoglobulin light chains extracted from the urine of patients with AL produce amyloid deposits when injected into mice. Conversely, the light chains from the urine of patients with multiple myeloma who do not have amyloid will not produce amyloid deposits on injection into mice [4]. It is thought that amyloidogenic light chains, because of amino acid substitutions, assume a greater propensity to form a β-pleated sheet, the ultrastructure of the

Table 1. Nomenclature for amyloidosis

Protein	Precursor	Clinical features
AL or AH	Immunoglobulin light or heavy chain	Primary or localized; associated with myeloma or macroglobulinemia
AA	Serum amyloid A	Secondary or familial Mediterranean fever
ATTR	Transthyretin	Familial and senile
A fibrinogen	Fibrinogen	Familial renal amyloidosis (Ostertag)
Aβ2M	β2 microglobulin	Dialysis-associated carpal tunnel syndrome
Aβ	Amyloid β protein	Alzheimer's disease

amyloid fibril. Further supporting an amyloidogenic structure of amyloid light chains is that, in multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS), λ-immunoglobulin light chains account for two-thirds of the immunoglobulin proteins. In amyloidosis, λ-immunoglobulin light chains represent 75% of the deposits. The λ_{VI} subclass of immunoglobulin light chains seems to be associated uniquely with amyloid. Patients with AL may be classified into those with multiple myeloma and those without multiple myeloma. This classification is determined by the percentage of plasma cells in the bone marrow, the presence or absence of lytic skeletal lesions, and whether renal insufficiency is present as a result of amyloid as opposed to myeloma cast nephropathy. True multiple myeloma is uncommon in amyloidosis and accounts for fewer than 10% of all AL. If a patient does not have myeloma at the time AL is diagnosed, the likelihood of myeloma developing is one in 250 [5•].

The median age of all patients with AL at the Mayo Clinic is 62 years. The incidence of amyloidosis in Olmsted County, MN, is eight per one million people annually. This number is comparable with the incidence of agnogenic myeloid metaplasia, polycythemia rubra vera, or Hodgkin's disease [6,7]. The incidence of multiple myeloma is four times that of AL. AL is a monoclonal gammopathy with few monoclonal plasma cells seen in the bone marrow. The disease is frequently confused with multiple myeloma.

The symptoms and physical findings seen in patients with amyloidosis are generally nonspecific and seen in only a minority of patients. Only 1% of patients are younger than 40 years of age. Males represent nearly two-thirds of all patients. In multiple myeloma, males constitute 52% of the patients. The two most common symptoms in patients with amyloidosis are fatigue and weight loss. These symptoms lead to an investigation for an underlying occult malignancy, which is a fruitless endeavor in a patient with amyloidosis [8]. Light-headedness, again nonspecific, will accompany fatigue. The etiology of light-headedness is generally the contraction of plasma volume in patients with nephrotic syndrome or low stroke volume in patients who have restriction to ventricular inflow during diastole. Orthostatic hypotension is a regular accompaniment of renal or cardiac amyloidosis. In patients who have autonomic neuropathy associated with amyloid peripheral neuropathy, orthostatic hypotension is a consequence of autonomic failure.

Physical findings that are diagnostic of amyloidosis are seen in only a few patients. Diagnostic periorbital or facial purpura is present in 10% to 15% of patients. The purpura occurs above the nipple line, typically in the webbing of the neck, eyelids, or face. A liver edge more than 5 cm below the right costal margin is seen in 10% of all patients. Macroglossia is seen in 10% of patients and frequently can be overlooked because the enlargement tends to occur on the underside of the tongue. Submandibular salivary gland enlargement is common but is frequently misinterpreted as small submandibular lymph nodes. Rarely, patients with amyloidosis have symptoms suggestive of temporal arteritis [9,10]. Amyloid can occlude smaller vessels, leading to ischemia and symptomatic calf, shoulder, buttock, or jaw claudication. Empiric therapy with corticosteroids will not help and will delay the correct diagnosis [11]. Skeletal muscle pseudohypertrophy can produce shoulder pad sign. Most patients with amyloid muscle involvement are weak as a result of muscular atrophy from chronic occlusion of vessels serving the muscles, and subsequent atrophy [12]. A dry mouth is common due to infiltration of the minor salivary glands [13]. In the absence of a biopsy of the minor salivary glands, Sjögren's syndrome can be misdiagnosed [14].

CLASSIFICATION

An accurate classification of the type of amyloidosis is critical to avoid unnecessarily exposing a patient without a plasma cell dyscrasia to cytotoxic chemotherapy. Nearly 99% of patients with AL have a monoclonal light chain in the serum or urine or a clonal population of plasma cells in the bone marrow detectable by immunohistochemistry or immunofluorescence. Occasionally, physicians use immunohistochemical staining of the amyloid deposits. If a patient has amyloidosis but no evidence of a plasma cell dyscrasia, it must be determined whether the amyloidosis is localized. When amyloid is seen in the

bladder, ureter, or urethra, localized genitourinary amyloidosis is more likely than systemic AL. Amyloidosis found in the vocal cords, trachea, or mainstem bronchi is generally localized. A pulmonary nodule thought to represent malignancy subsequently demonstrated to be amyloid is generally not part of a systemic amyloid syndrome. Most patients with cutaneous amyloidosis have a localized form.

Patients with a systemic or visceral amyloid syndrome, such as nephropathy, cardiomyopathy, or peripheral neuropathy in the absence of a detectable M protein or plasma cell dyscrasia, may have AA or AF. AA is rare in the Western hemisphere. Juvenile rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis are the disorders most commonly associated with AA. Patients with AA have had a rheumatic disorder for 15 years and then develop proteinuria. In patients with AA, the most common clinical presentation is nephrotic-range proteinuria followed by amyloid involvement of the bowel.

Familial amyloidosis is second to AL in causing a systemic or visceral amyloid syndrome. Almost 50% of the patients with AF do not have a family history. Patients with AF can have peripheral neuropathy usually caused by a mutant transthyretin (TTR). We have seen patients with AF of the kidney caused by mutations in fibrinogen or lysozyme.

Transthyretin amyloidosis of the heart can occur with no mutations in elderly patients. The clinical presentation is restrictive cardiomyopathy with congestive heart failure in patients older than 60 years of age. The deposits of amyloid stain immunohistochemically with antitransthyretin. There is no plasma cell dyscrasia. The TTR gene must be sequenced for a mutation before making the diagnosis of this so-called senile cardiac amyloidosis. These diagnostic studies are indicated in patients who do not have a plasma cell dyscrasia, which is always associated with AL.

AMYLOID SYNDROMES

The most common amyloid syndromes are nephrotic-range proteinuria with or without renal insufficiency, hepatomegaly, restrictive cardiomyopathy, and peripheral neuropathy (Table 2) [15,16,17•,18]. When a patient has unexplained proteinuria, hepatomegaly, heart failure, or neuropathy, the initial screening should include immunofixation of the serum and urine [19]. Detection of a free monoclonal immunoglobulin confirms the suspicion of amyloidosis [20]. Many patients with AL have only free light chains in the serum. As a result, light chains will not accumulate in the serum in sufficient amounts to produce an M spike on serum protein electrophoresis. Immunofixation is required for its detection. A screening serum protein electrophoresis is inadequate because it will not detect one-third of the patients with a small monoclonal protein in the serum.

Almost 50% of the patients with AL have more than 1 gram of albumin in the urine. The excretion of large amounts of plasma proteins into the urine obscures the small amounts of free monoclonal light chain present. Because no peak is visible in the urine, immunofixation is required. If the urine and serum are screened in patients with AL, an M component will be found in nearly 90%. Immunofixation of the serum and urine is the best noninvasive screening study when a clinician is evaluating a patient with any of the four clinical syndromes described earlier (Table 2) [18]. In the 10% of patients without a detectable M component, a clonal population of plasma cells can virtually always be detected in the bone marrow. These patients with a clonal population of amyloid-producing plasma cells but no immunoglobulin light chain in the serum or urine represent the counterpart of nonsecretory multiple myeloma and could be referred to as having nonsecretory AL [21,22].

DIAGNOSIS AND PROGNOSIS

Amyloid deposits can be demonstrated in vivo by scanning with radiolabeled amyloid P component. Amyloid deposits always contain amyloid P component, a pentagonal glycoprotein dimer that comprises approximately 10% of the amyloid fibril by weight [23]. These scans do not recognize small deposits and are incapable of visualizing cardiac amyloid deposits. The diagnosis of amyloid requires the demonstration in biopsy tissues of deposits that bind Congo red. Patients with renal, cardiac, hepatic, or peripheral nerve amyloid can always have the diagnosis confirmed by direct biopsy of these organs [24]. However, biopsy of these organs is not required to establish the diagnosis (Table 3).

Biopsy of tissues that contain blood vessels frequently demonstrates amyloid deposits even when there is no clinical evidence of involvement at those sites. Biopsy of minor salivary glands from the lip has been reported to demonstrate amyloid in 85% of patients [25]. Biopsy of clinically uninvolved skin demonstrates amyloid deposits in the vessels of the subcutaneous tissues [26••]. The results of rectal biopsy result are positive in 80% of patients, including in those with no symptoms referable to the gastrointestinal tract. The rectal biopsy is not used as frequently because bleeding from the rectum can occur.

Our practice is to obtain a biopsy of the bone marrow and the subcutaneous fat tissues simultaneously. Each technique yields the diagnosis in 50% and 80%, respectively. Together, the bone marrow and the fat aspirate can establish the diagnosis in 90% of patients. A bone marrow specimen is required in any case to exclude the presence of multiple myeloma. In the remaining 10% of patients in whom the subcutaneous fat and bone marrow biopsy results are negative, a direct biopsy of the

Table 2. Syndromes in primary amyloidosis (AL)

Syndrome	Patients, %
Nephrotic syndrome or renal failure	30
Hepatomegaly	24
Congestive heart failure	22
Carpal tunnel syndrome	21
Neuropathy	17
Orthostatic hypotension	12

affected organ yields the diagnosis. Caution must be exercised when interpreting Congo red-stained tissues. False-positive results are seen because of dye precipitation.

The cause of death in most patients with amyloidosis is cardiomyopathy that progresses to congestive heart failure or sudden death due to fibrillation or asystole [27]. The clinical outcome in amyloidosis depends on the extent of cardiac involvement. Echocardiography is a routine part of the assessment of all patients with AL [28]. In our experience, the presence of symptomatic congestive heart failure has been the most powerful indicator of survival in the multivariate model [29]. The presence of syncope is a powerful predictor of imminent sudden death [30]. When exertional syncope is present, the patient should be evaluated for the placement of an implantable defibrillator.

The Doppler-derived index of diastolic myocardial performance is important in assessing the prognosis of patients with amyloid [31]. The most significant echocardiographic predictors of outcome are the Doppler index of diastolic myocardial performance, ejection fraction, and mitral deceleration time, a reflection of the ability of the ventricle to relax.

The value of Doppler-derived diastolic filling variables for assessing prognosis cannot be overemphasized [32]. Patients with a deceleration time of 150 milliseconds or less on Doppler echocardiography, which indicates restrictive physiology, have a 1-year probability of survival of 49% versus 92% in those with a deceleration time greater than 150 milliseconds [33].

The time between histologic diagnosis and referral is an important variable. In all patients with amyloidosis at the Mayo Clinic, the median survival time is nearly 2 years. However, when only patients seen within 30 days of diagnosis are included, the median survival time is approximately 13 months.

The presence of peripheral neuropathy as a dominant syndrome is associated with improved outcome. Neuropathy is associated with a 3-year median survival time, but only when patients with congestive heart failure, nephrotic syndrome, and orthostatic hypotension are excluded.

Treatment

- The definition of a response in amyloidosis can be organ-based or hematologic. In patients with renal amyloidosis, an organ-based response requires a 50% reduction in urinary protein excretion without an increase in the serum creatinine level. In patients with dominant hepatic involvement, a reduction in the serum alkaline phosphatase level by 50% is considered a response. In patients with cardiac amyloidosis, a 2-mm reduction in the echocardiographic thickness reflects a response. Improvement in peripheral neuropathy or echocardiographic ejection fraction is rare. Hematologic responses in amyloidosis follow the criteria previously established for multiple myeloma. For patients who have a measurable M peak in the serum or urine, a hematologic response requires a 50% reduction in the size of the peak. A high proportion of patients have small quantities of free light chains in the serum or urine that cannot be quantified. A response requires the complete eradication of the light chain, proven by immunofixation. Because the bone marrow plasma cells average approximately 5%, it is difficult to obtain a visual estimate that can confirm a 50% reduction in the number of plasma cells. Patients who fulfill these response criteria have substantially longer survival times.
- Patients appear to derive the most benefit when the response is organ-based. Our experience suggests that most patients who achieve an organ-defined response also demonstrate a hematologic response. Treatment-induced regression of the clonal plasma cell dyscrasia results in decreased production of amyloidogenic light chains, which over many months is accompanied by improved organ function.

Table 3. Diagnostic pathway for primary amyloidosis (AL)

Consider AL in patients with:	Nephrotic-range proteinuria (nondiabetic)
	Cardiomyopathy (no ischemic history)
	Hepatomegaly (no filling defects by imaging)
	Peripheral neuropathy (nondiabetic)
Increase suspicion	Immunofixation of serum and urine
Confirm diagnosis histologically	Fat aspirate and marrow biopsy stain with Congo red (90% sensitive)
Assess prognosis	Echocardiography required (Doppler important)
Treat	Melphalan and prednisone
	High-dose steroids
	Stem cell transplantation
	Organ transplantation

(*Adapted from* Gertz *et al.* [50].)

Diet and lifestyle

- Appropriate dietary changes are needed for patients with nephrotic range proteinuria, renal failure, heart failure, or liver dysfunction. These modifications are nonspecific to amyloidosis but similar to other causes of such organ dysfunction.

Pharmacologic treatment

Alkylating agents

Treatment of AL with alkylating agent-based chemotherapy has been shown to improve survival in two prospective randomized studies [34,35]. In patients who demonstrate an organ-based response to melphalan and prednisone chemotherapy, the median survival time can approach 90 months [36]. However, even with alkylating agent-based chemotherapy, 36% of patients die within 1 year of diagnosis. With alkylating agent-based chemotherapy, the overall impact on survival is minimal. Even when the production of precursor light chain is eliminated, many patients die of end-organ damage. In our experience, the median time to obtain an organ-based response is 1 year. After stem cell transplantation, we have seen six responses taking more than 1 year to manifest; one response was not seen until 28 months after therapy. Many patients, particularly those with cardiac involvement, will not live long enough to respond.

Standard dosage Melphalan 0.15 mg/kg daily for 7 days, with prednisone 0.8 mg/kg daily for the same 7 days. Treatment cycles are repeated every 6 weeks, monitoring the leukocyte and platelet count every third week.

Contraindications Very poor performance status or severe cytopenias.

Main side effects Because of the chronic myelosuppressive nature of melphalan, many patients develop chronic, long-standing granulocytopenia and thrombocytopenia. After the cessation of melphalan, many patients remain leukopenic for 1 year. As with any alkylating agent, myelodysplasia or acute leukemia can develop as a result of chromosome damage induced by melphalan [37]. Characteristic cytogenetic abnormalities, including deletions of chromosomes 5 and 7, can be seen in up to 7% of patients exposed to melphalan. The median survival time from the onset of myelodysplasia is 8 months.

Special points With melphalan and prednisone chemotherapy, statistically significant survival benefit is seen. This benefit translates to a 17-month median survival time for patients treated with melphalan compared with 12 months for patients treated with colchicine. Melphalan and prednisone is considered the standard therapy for AL, but alternatives need to be found because of the poor survival rate.

Cost effectiveness Undetermined; melphalan and prednisone are relatively inexpensive.

Other pharmacologic treatments

- We have tested α-tocopherol [38] and interferon-α2 [39] and found neither to be effective.
- High-dose dexamethasone combined with interferon has been reported to be effective in a high proportion of patients with amyloidosis without cardiac involvement [40]. Dexamethasone does not cause myelodysplasia. In addition, its toxicity is reversible on its cessation. We have treated 44 patients with high-dose dexamethasone. Responses were seen in only 18% of the patients. The responses that occurred were clinically important. Several patients remain on maintenance dexamethasone 5 years after diagnosis and have a good quality of life. Of the 44 patients, 11 are alive (median 47 months). Part of the reason for the poor response rate was a high proportion of patients with cardiac amyloid. Treatment with dexamethasone was associated with bowel perforation, disseminated herpes zoster, and streptococcal sepsis. We consider dexamethasone as an option if other alternatives do not exist.
- Chemotherapy with vincristine, adriamycin, and dexamethasone (VAD) has been used to treat amyloidosis. One patient with amyloid nephrotic syndrome received four cycles of VAD, during which time proteinuria diminished rapidly. VAD can improve the condition of patients with AL and reduce transplant morbidity and mortality rates [41••].
- An iodinated anthracycline analog, iodo-deoxydoxorubicin, has been reported to be effective in dissolving amyloid deposits [42]. It has been shown to bind and result in the rapid dissociation of mutant transthyretin crystals [43•]. With electron microscopy, iodo-deoxydoxorubicin can be shown to disrupt the fibrillar structure of transthyretin amyloid into an amorphous material [44•]. It is most effective in patients with soft tissue deposits. The response rate is less well-defined for patients with visceral amyloid deposits, such as the liver, kidney, and heart.
- The role of thalidomide, an agent known to be active in multiple myeloma, is unknown in amyloidosis.
- In a prospective randomized study of 101 patients, we treated 50% with traditional melphalan and prednisone and the other 50% with the five-drug regimen of vincristine, bischloroethylnitrosourea, melphalan, cytoxan, and prednisone (VBMCP) [45•]. No survival advantage was seen for the five-drug combination compared with the standard treatment.

Transplantation

Cardiac transplantation

- Cardiac transplantation for patients with severe cardiac amyloidosis is investigational.
- An initial report suggested that the long-term outcome of cardiac transplantation for patients with AL was poor. There have since been reported survival times of 69 and 118 months after cardiac transplantation [46,47]. At the Mayo Clinic, 13 patients with amyloid heart disease were accepted for transplantation. Eight patients have undergone transplantation, with one patient waiting. Three patients died while on the waiting list, while one was removed from the list because of multi-organ failure. The 1-year survival rate after transplant was 100%. The 2-year survival rate after transplant was 83.3%. One patient died of disseminated multi-organ amyloid 16 months after transplantation. Another patient died of a lymphoproliferative disorder 31 months after transplantation. Six patients are alive with

a median follow-up of 43 months. Nephrotic syndrome developed in two of the six patients after transplant; one received a renal transplant. Two patients subsequently received stem cell transplants in an effort to prevent recurrence of amyloid in the transplanted heart; both are alive. The survival rate in cardiac transplant patients with amyloidosis is 50% at 5 years.

Stem cell transplantation

- Considering the poor results obtained with standard chemotherapy and the improved complete response rates and increased survival times that have been demonstrated with stem cell transplantation for multiple myeloma, it was inevitable that this technique would be applied to patients with amyloidosis. Most patients who come to transplantation with a hematologic malignancy have no visceral dysfunction. Most protocols require satisfactory cardiac and pulmonary function with a good performance status. However, patients with amyloidosis have significant renal, cardiac, or hepatic dysfunction, which makes this group distinct from other candidates for stem cell transplantation.
- Boston University reported on 25 patients who underwent mobilization using granulocyte colony-stimulating factor (G-CSF) alone; melphalan was administered for conditioning at a dose of 200 mg/m^2. The median age was 48 years, with 88% having a performance status of 1 or 2. Eight of the patients had cardiac amyloidosis, but none had congestive heart failure. Ten had three or more organ systems involved. Seventeen of the 25 patients (68%) were alive at 24 months. Thirteen of 21 (62%) evaluable patients had a hematologic response. Eleven of 17 (65%) had improvement of their amyloid-related organ involvement. Three patients subsequently relapsed between 12 and 24 months. Proteinuria was reduced in nine patients with renal involvement. Neuropathy was resolved in two of three patients. Adverse predictors of survival included more than two major organ systems involved at the time of transplant, and predominant cardiac involvement. Two patients died after stem cell collection before receiving conditioning chemotherapy. When the data were updated to 102 patients, the median age of patients was 55 years. Older patients and patients with reduced cardiac or renal function were administered half-dose melphalan. The 3-month treatment-related mortality rate was 15%. The survival rate in patients with predominantly cardiac involvement was 33% compared with 83% for renal patients. The rate of hematologic response was 55%.
- We have transplanted 97 patients with amyloidosis and have follow-up data for our first 66 [48••]. Forty-five of the 66 patients had dominant renal amyloidosis. Forty-five patients had echocardiographic evidence of amyloidosis. Conditioning involved melphalan (140 mg/m^2) and total body irradiation (12 Gy) in 17 patients, melphalan (200 mg/m^2) in 38, and melphalan in 11 (100 or 140 mg/m^2). Stem cells were mobilized by using G-CSF at 10 μg/kg daily or by using cyclophosphamide 3 grams/m^2 followed by G-CSF 5 μg/kg daily. G-CSF 10 μg/kg daily has resulted in fewer aphereses (median 2) to achieve our target goal of 5 × 10^6 CD34+ cells/kg.
- Engraftment is not a problem with stem cell transplantation. A neutrophil count of greater than 500/μL was achieved in all but one patient who died on day 6. Six patients died without having recovered a platelet count of 20,000/μL. Sixty patients had a nontransfused platelet count in excess of 20,000/μL (median day 14). Of the 66 patients, 14 have died, nine before day 100, for a treatment-related mortality rate of 14%. The remaining five died of progressive cardiac amyloid, from failing to respond to transplant

Table 4. Guidelines for selecting patients for stem cell transplantation

Absolute contraindications	Relative contraindications
Clinical congestive heart failure	Serum creatinine > 2.0 mg/dL
Total bilirubin count > 3.0 mg/dL	Interventricular septal thickness > 15 mm
Echocardiographic ejection fraction < 45%	Age > 60 years
	More than two visceral organs involved

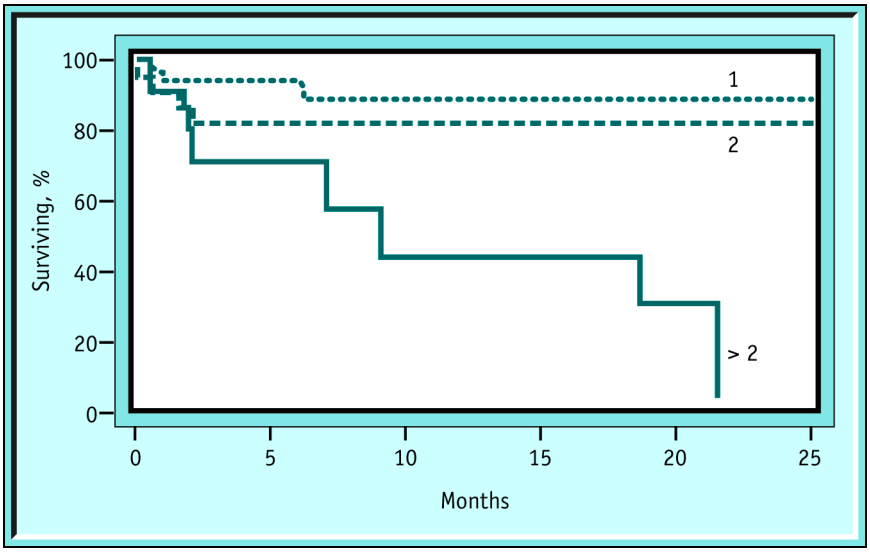

Figure 1. Kaplan-Meier survival rate of transplanted patients with amyloidosis based on the number of organs involved (one, two, or more than two).

(n = 4) or from progressive amyloidosis after an initial response (n = 1). The treatment-related mortality rate includes cardiac asystole, multi-organ failure after conditioning, aspiration pneumonia from amyloid autonomic neuropathy, and progressive cardiac failure. *Staphylococcus* bacteremia after transplantation is common. Cardiac arrhythmias are seen regularly during collection and transplantation. Marked gastrointestinal tract toxic responses, including severe bleeding and prolonged anorexia requiring nutritional support, are seen.

- There were 32 hematologic responses and 31 organ responses for an overall response rate of 41 of 66 (62%). The responses were renal in 19 patients, hepatic in five, cardiac in three, renal and cardiac in two, renal and hepatic in one, cardiac, renal, and neuropathy in one, and autonomic neuropathy in one. The median time to a response was 3.6 months, but a response was not demonstrable until after 1 year in six renal patients. One response was not seen until 28 months after therapy. The 2-year actuarial survival rate of all the patients is 70%. Table 4 includes the guidelines we are using for the selection of patients for consideration for stem cell transplantation.
- Blood stem cell transplants for patients with amyloidosis have a much higher morbidity and mortality rate than transplants for patients with myeloma [48••]. In our program, five of the six patients who died had cardiac failure. The best results are achieved in patients with isolated renal amyloidosis (Fig. 1).
- Patients receiving transplants for amyloidosis are a highly selected group by virtue of their age, performance status, number of organs involved, and the absence of important cardiac involvement. It is uncertain what the survival of a comparable control group would be, because no randomized trials exist.

On reviewing the Mayo Clinic's amyloid database from 1983 through 1997 to select those patients who would theoretically be eligible for stem cell transplantation, 234 of 1288 patients met the eligibility criteria of age younger than 70 years, ventricular septal thickness less than 15 mm, ejection fraction greater than 55%, creatinine concentration less than 2 mg/dL, and alkaline phosphatase less than three times the normal. Heart, liver, and nerve involvement were present in 42%, 6%, and 16% of patients, respectively [49••]. The median survival time was 45.6 months. For patients younger than 50 years of age, 51 to 60 years of age, and 61 to 70 years of age, the median survival times were 61, 46, and 30 months, respectively. Patients eligible for a stem cell transplantation are inherently a good-risk population with a superior median survival rate.

- The response rates in patients with amyloidosis who receive a stem cell transplantation appear to be higher than those seen in patients treated with melphalan and prednisone. The morbidity and mortality rates associated with the procedure are higher. There is a high rate of gastrointestinal tract toxic responses, with a high prevalence of hemorrhage. Cardiac arrhythmias are common. Because patients eligible for transplantation have a better prognosis, outcomes must be compared with a matched control group.

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