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REVIEW ARTICLE

Amyloidosis: Pathogenesis and New Therapeutic Options

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The systemic amyloidoses are a group of complex diseases caused by tissue deposition of misfolded proteins that results in progressive organ damage. The most common type, immunoglobulin light chain amyloidosis (AL), is caused by clonal plasma cells that produce misfolded light chains. The purpose of this review is to provide up-to-date information on diagnosis and treatment options for AL amyloidosis. Early, accurate diagnosis is the key to effective therapy, and unequivocal identification of the amyloidogenic protein may require advanced technologies and expertise. Prognosis is dominated by the extent of cardiac involvement, and cardiac staging directs the choice of therapy. Treatment for AL amyloidosis is highly individualized, determined on the basis of age, organ dysfunction, and regimen toxicities, and should be guided by biomarkers of hematologic and cardiac response. Alkylator-based chemotherapy is effective in almost two thirds of patients. Novel agents are also active, and trials are ongoing to establish their optimal use. Treatment algorithms will continue to be refined through controlled trials. Advances in basic research have led to the identification of new drug targets and therapeutic approaches, which will be integrated with chemotherapy in the future.

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INTRODUCTION

An increasing number of diseases are recognized to arise from the failure of proteins to adopt functional conformational states. These pathologic conditions are generally referred to as protein misfolding (or protein conformational) diseases. The largest group of misfolding diseases is associated with the conversion of peptides or proteins from their soluble functional states into highly organized fibrillar aggregates showing a cross-beta super-secondary structure termed "amyloid."[1] This is a complex process involving key players from the intracellular protein quality control system, extracellular chaperones and matrix components, proteases, and other cofactors. Although this process is still under intense investigation, advances have been made during the last decade in deciphering the molecular mechanisms underlying protein misfolding, aggregation, and fibril formation that have led to the development of novel drugs targeting specific steps of the amyloid cascade (Fig 1). Ideally, the treatment of amyloid diseases should exploit synergizing approaches and strategies to reduce precursor protein production, prevent misfolding and fibril formation, and promote the reabsorption of amyloid deposits. Some of these treatments are currently being tested in animal models and clinical trials and will become available to the clinician in the near future.

Amyloid Proteins and Amyloid Diseases

The amyloidoses differ in the protein precursor undergoing aggregation, the target organs involved in amyloid deposition and, consequently, in their clinical features. To date, at least 28 different proteins have been identified as causative agents of amyloid diseases, ranging from localized cerebral amyloidosis in neurodegenerative conditions such as Alzheimer's and Creutzfeldt-Jakob diseases, to systemic amyloidoses such as immunoglobulin (Ig) monoclonal light chain amyloidosis (AL) and transthyretin (ATTR) amyloidosis.[8] Table 1 summarizes the six most common forms of systemic amyloidoses. The amyloidogenic proteins are synthesized by various organs and require distinct therapeutic approaches. It is therefore essential to unequivocally identify the protein responsible for the disease before embarking on therapy that can be as momentous as a liver transplantation or hematopoietic stem-cell transplantation (SCT). The most common form of systemic amyloidosis is AL amyloidosis, with a reported incidence of 8.9 per million person-years.[9] AL amyloidosis is of interest to the oncologist because it is caused by a neoplastic plasma cell or B-cell clone; furthermore, its prevalence among the plasma cell dyscrasias has increased in recent years because of the extended survival achieved with new effective therapies. It is noteworthy that reactive or secondary amyloidosis can occasionally occur in patients with other neoplasms (hepatocellular carcinoma, renal cell carcinoma,

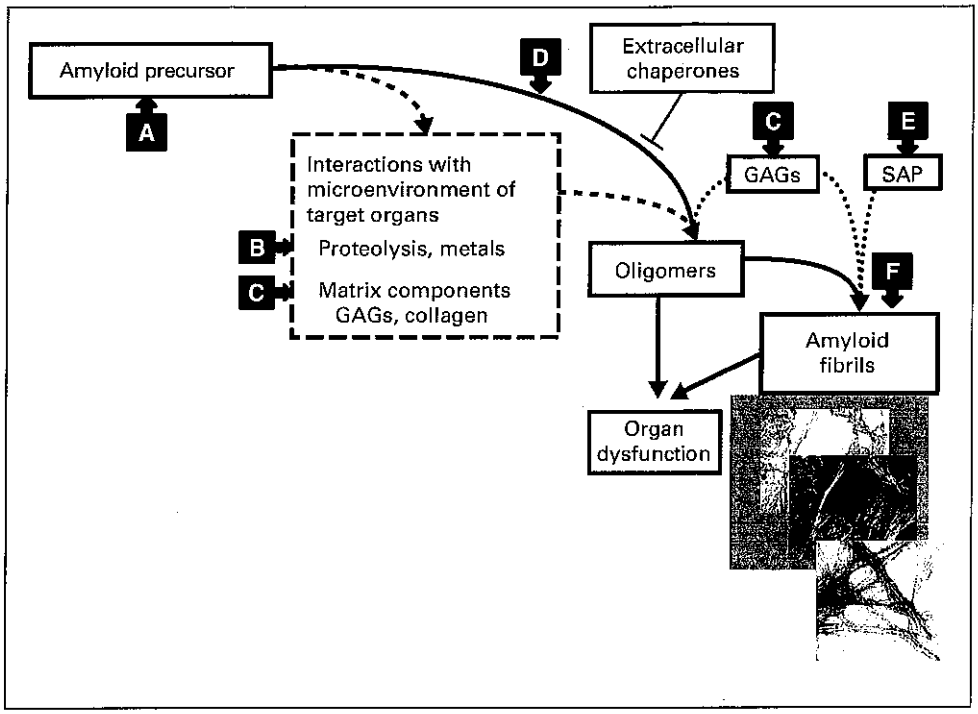

Fig 1. The cascade of molecular events leading to amyloidosis. The amyloidogenic precursor may trigger amyloid formation when its concentration increases in serum or because a mutation favors misfolding. Some normal proteins with an intrinsic amyloidogenic predisposition can, at a low rate, form amyloid deposits that become symptomatic in the elderly (eg, wild-type transthyretin causing senile systemic amyloidosis). Interaction with the extracellular environment may result in proteolytic cleavage and binding to matrix components such as glycosaminoglycans (GAGs) and collagen that facilitate aggregation. Several lines of evidence support a role for extracellular chaperones in the in vivo clearance of aggregation-prone extracellular proteins. In some types of systemic amyloidosis, such as immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), oligomers may be the major cytotoxic species. Serum amyloid P (SAP) binds to amyloid fibrils and protects them from reabsorption. The amyloid deposits exhibit a characteristic affinity for Congo red staining with brilliant green birefringence under polarized light and are formed by 10- to 12-nm–wide nonbranching fibrils, as observed by electron microscopy. (A) The synthesis of the amyloidogenic precursor may be eliminated by using chemotherapy in AL amyloidosis or liver transplantation in ATTR amyloidosis; silencing by using RNA interference is being tested in animal models. (B) Inhibitors of proteases (secretase) and metal protein–attenuating compounds are being evaluated in trials. (C) Compounds interfering with the binding of GAGs to the amyloid proteins (eprodisate) have been successful in secondary amyloidosis.[2] (D) Small molecules capable of stabilizing the amyloid precursor and preventing its misfolding and aggregation (diflunisal, tafamidis)[3] are being tested in ATTR amyloidosis. (E) SAP can be cleared from amyloid deposits by using small palindromic drugs.[4] (F) The clearance of amyloid deposits can be promoted and accelerated by specific antibodies through passive[5] and active immunotherapy,[6] or by combining small palindromic drugs with anti-SAP antibodies.[7]

Castleman's disease, Hodgkin's disease, adult hairy cell leukemia). Other forms of amyloidosis listed in Table 1 are relevant for consideration of differential diagnosis.[10-12]

Mechanism of Tissue Damage

The process of amyloid formation results in cellular injury, tissue damage, and organ dysfunction through mechanisms that are incompletely understood. The simple explanation of a physical, mechanical replacement of parenchymal tissue by amyloid deposits seems to be insufficient. A growing body of literature has implicated prefibrillar oligomers, rather than the fibrillar form, as the primary pathologic species of Alzheimer's disease[13] and ATTR amyloidosis.[14] Direct cytotoxicity of amyloidogenic Ig light chains to cardiac cells has also been demonstrated.[15] Thus, organ damage may occur through two intermingled mechanisms. The relative impact of amyloid deposits or prefibrillar aggregates on cytotoxicity and tissue dysfunction may vary among types of amyloidosis and among organs. For instance, clinical observations of patients with AL amyloidosis demonstrated that the reduction of the amyloidogenic free light chain concentration following chemotherapy translated into a reduction of the serum concentration of the amino terminal fragment of pro-brain natriuretic peptide (NT-proBNP), a marker of cardiac dysfunction, despite unaltered amyloid deposits in the myocardium as assessed by echocardiography. The reduction of NT-proBNP was associated with improved cardiac function and extended survival.[16,17] These findings indicate that in AL amyloidosis, the amyloid precursor (the free light chain) plays an important role in tissue dysfunction and that it is essential to eliminate its production in the shortest possible time.

CLINICAL FEATURES OF AL AMYLOIDOSIS

Clinical and Genetic Features of Plasma Cell Dyscrasias and Their Associated Igs

Clinical and laboratory findings distinguish monoclonal gammopathy of undetermined significance (MGUS), myeloma, and AL amyloidosis. Patients with MGUS are asymptomatic, and the finding of a monoclonal Ig in the serum or urine is incidental. Patients with myeloma generally have a high plasma cell burden in the bone marrow, accompanied by symptoms and signs of hypercalcemia, renal insufficiency, anemia, and lytic bone lesions. Patients with amyloidosis usually present with a small plasma cell clone with evidence of

Table 1. Most Common Types of Systemic Amyloidoses

Type	Abbreviation	Precursor	Site of Synthesis	Syndrome and Organs Involved
Immunoglobulin light chain amyloidosis	AL	Monoclonal light chain	Bone marrow plasma cells	Primary, can occur in 10% to 15% of patients with multiple myeloma Involvement of heart, kidneys, liver, GI tract, peripheral nerves, autonomic nerves, soft tissues
Reactive amyloidosis	AA	Serum amyloid A	Liver	Secondary to chronic inflammation, infection, or certain neoplasia Involvement of kidneys, GI tract, spleen, liver, autonomic nerves
Senile systemic amyloidosis	SSA	Transthyretin wild-type	Liver > 90%	Age related, usually males (age > 65 years) Primarily cardiac involvement
Transthyretin amyloidosis	ATTR	Variant transthyretin, > 100 amyloidogenic mutations	Liver > 90%	Hereditary Involvement of peripheral nerves, autonomic nerves, heart, eye, leptomeninges, rarely kidneys
Fibrinogen amyloidosis	AFib	Variant fibrinogen α chain	Liver	Hereditary Involvement of kidneys
Apolipoprotein A-I amyloidosis	AApoAI	Variant apolipoprotein AI	Liver, intestine	Hereditary Involvement of heart, liver, kidneys, skin, larynx, testes

dysfunction of one or more involved organs.[18] Typical AL amyloidosis syndromes include renal involvement (approximately 70% of patients) with nephrotic range proteinuria or renal failure in approximately 50%; cardiomyopathy in approximately 60% with thick-walled heart, low voltage on ECG, and pericardial and pleural effusions; cholestatic hepatopathy (approximately 25%); peripheral neuropathy (approximately 20%) and autonomic neuropathy (approximately 15%); infiltration of soft tissues, of which macroglossia (approximately 15%) is a pathognomonic finding; and purpura, including periorbital ecchymoses (approximately 10%) due to capillary involvement and/or clotting factor deficiency.

Although patients with MGUS and those with multiple myeloma typically have an "M" or monoclonal peak on serum protein electrophoresis, patients with AL amyloidosis often have little intact monoclonal Ig; approximately 40% of patients have light chains only and about half the patients are missed if only serum protein electrophoresis is used for screening. Immunofixation electrophoresis to identify a κ or λ light chain is more sensitive, and the combination of serum and urine immunofixation electrophoresis with serum free light chain (FLC) assay approaches 100% sensitivity for identifying a monoclonal protein in patients with AL amyloidosis.[19] Free Ig light chains are accurately quantified by nephelometry, they have a much shorter half-life in the circulation than intact Igs, and they are useful for monitoring early responses to antiplasma cell chemotherapy. Because free light chains are cleared by the kidney, renal insufficiency will increase their concentrations. In that case, the FLC κ:λ ratio or the difference between involved and uninvolved free light chains should be monitored.[20]

The amino acid sequence of the highly polymorphic light chain may determine its likelihood of forming amyloid and also its target organ.[21-23] Aside from the light chain selection, no phenotypic or genetic features have been identified that distinguish AL amyloidosis from other plasma cell dyscrasias. Neither cytogenetics nor fluorescent in situ hybridization identifies chromosomal aberrations that distinguish MGUS from AL amyloidosis. It has been reported that increased cyclin D1 (*CCND1*) expression is associated with production of FLCs only, cardiac involvement, and possibly IgVL gene selection bias.[24] AL plasma cells express the low-affinity IgG Fc receptor CD32B[25] and calreticulin, a pleiotropic calcium-binding protein, and a significant proportion (40%) may express CD20.[26] These represent new potential targets for AL amyloidosis immunotherapy.

Diagnosis and Differential Diagnosis

AL amyloidosis should be suspected in any patient with nondiabetic nephrotic syndrome, nonischemic cardiomyopathy with an echocardiogram showing concentric hypertrophy, increase of NT-proBNP in the absence of primary heart disease, presence of hepatomegaly or increase of alkaline phosphatase without an imaging abnormality, peripheral and/or autonomic neuropathy, or unexplained facial or neck purpura or macroglossia. Any patient who presents with any one of these syndromes should undergo a biopsy to detect amyloid deposits and a screening for monoclonal Ig light chains. If a monoclonal protein is present, a bone marrow examination should be performed to exclude the presence of multiple myeloma. A bone marrow biopsy is also useful for Congo red staining, because the stroma or blood vessels will be positive for amyloid in > 60% of patients.[27] Congo red staining of subcutaneous fat obtained by aspiration is a reliable and noninvasive test that will identify amyloid deposits in approximately 90% of patients.[28] If negative, a biopsy of the labial salivary glands may detect amyloid deposits in 50% of patients; if this is also negative, then an involved organ should be biopsied when the clinical index of suspicion is high. Patients with amyloid in the skin, larynx, GI tract, urinary tract, or in pulmonary nodules generally have localized amyloidosis, which usually remains localized.[29] All amyloid deposits contain a serum amyloid P (SAP) component, a glycoprotein that belongs to the pentraxin family. This property makes radiolabeled SAP a potentially useful diagnostic tool for imaging amyloid deposits and for monitoring therapy.[30] However, its availability is limited, and it fails to identify amyloid involvement of the heart.

If the patient has one of the clinical amyloidosis syndromes with an Ig light chain abnormality, it is important to exclude the possibility of senile systemic amyloidosis, particularly in older men

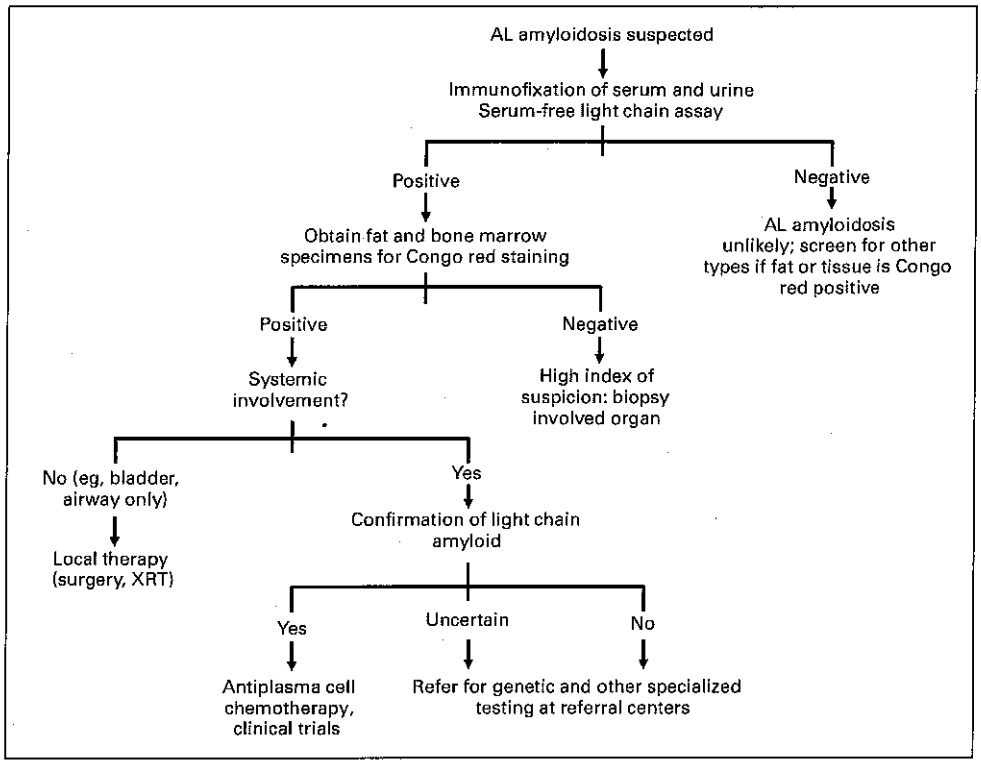

Fig 2. Diagnostic algorithm for systemic amyloidosis. Patients are generally referred to an oncologist or hematologist because they have a clinical syndrome consistent with immunoglobulin light chain amyloidosis (AL), or a monoclonal gammopathy with associated organ dysfunction. If clinical suggestion of amyloidosis is high and the fat aspirate is negative, a biopsy of the labial salivary gland may detect amyloid deposits in 50% of patients; if this is also negative, then an involved organ (kidney, endomyocardium, GI tract) should be biopsied. Demonstration of amyloid fibrils in the absence of a clonal light chain should precipitate a genetic and immunohistochemical or biochemical work-up for hereditary or other types of amyloidosis. XRT, radiation therapy.

with isolated cardiac involvement, and of reactive or familial amyloidosis with an incidental MGUS.[10,12] The light chain composition of an amyloid deposit can be confirmed with immunohistochemistry, which may be unreliable in AL amyloidosis,[10] or with immunogold techniques.[31] Mass spectrometry can confirm the amyloid protein composition and will likely become the gold standard for identifying the protein forming amyloid deposits as it becomes more generally available.[32,33] Accurate diagnosis is essential because patients with familial amyloidosis may be eligible for liver transplantation or clinical trials with small molecules; chemotherapy is contraindicated for these patients. Patients with systemic amyloid deposits but no sign of a plasma cell clone may have familial or secondary amyloidosis, and specialized testing for these should be undertaken at referral centers. An algorithm for the diagnosis of amyloidosis is given in Figure 2.

Prognosis and Staging

The median survival of 868 patients with AL amyloidosis who were followed at the Pavia center was 3.8 years, with 27% of patients dying within 1 year from diagnosis and a 10-year cumulative proportion of 31% who survived. Death was due to cardiac amyloidosis in 75% of the 393 patients who died, including sudden death in 25%. Therefore, the major determinant of outcome in amyloidosis is the extent of cardiac involvement. Echocardiographic features of cardiac amyloidosis such as wall thickening, diastolic relaxation abnormalities, and reduced systolic function are associated with a poor outcome.[34] The prognostic value of longitudinal Doppler myocardial strain and strain rate measurements has been reported.[35,36]

More recently, cardiovascular magnetic resonance has been successfully used for the diagnosis and prognosis of amyloid cardiomyopathy.[37] Presence of and patterns of gadolinium enhancement have value in the diagnosis of amyloid cardiomyopathy. The prognostic significance of cardiovascular magnetic resonance parameters has been evaluated in relatively small cohorts, and comparative studies are needed in well-defined, large series.

Cardiac biomarkers provide a quantitative assessment of cardiac damage (troponin I or T) and wall strain (BNP, NT-proBNP) and are the most important predictors of outcome in amyloidosis.[38,39] By using the cutoffs of 0.035 μg/L for troponin T and 332 ng/L for NT-proBNP, patients were classified into three stages on the basis of whether both biomarkers were low (stage 1; 33% of patients), either biomarker was abnormal (stage 2; 37%), or both biomarkers were high (stage 3; 30%). The median survivals were 26.4, 10.5, and 3.5 months, respectively.[40] This staging system is now used to stratify patients who are registering for clinical trials. The use of cardiac biomarkers has been validated in patients treated with conventional[17,35,41,42] and high-dose chemotherapy.[35,43] The troponin level predicts early mortality following SCT, and high-sensitivity troponin is also a powerful prognostic marker.[17] High baseline FLC concentration is associated with poor outcome in patients undergoing SCT,[44] and FLC level has been combined with cardiac biomarkers[45] and other markers of plasma cell burden[46] in newly proposed staging systems. Many other prognostic factors reflecting burden of disease and organ dysfunction have been proposed but not validated prospectively.

THERAPY

Criteria for Hematologic and Organ Response

Early diagnosis is the key to effective therapy allowing reversal of the organ damage and better tolerability of adverse effects of therapy.

Table 2. Updated Hematologic and Organ Response Criteria

Response Type	Abbreviation	Criteria
Hematologic response		
Complete response*	CR	Negative serum and urine IFE, normal κ/λ ratio
Very good partial response*	VGPR	dFLC < 40 mg/L
Partial response	PR	dFLC decrease ≥ 50%
No response	NR	Other
Organ response†		
Heart		Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by two New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness and/or a reduction (≥ 30% and ≥ 300 ng/L) of NT-proBNP in patients in whom the eGFR is ≥ 45 mL/min/1.73 m^2
Kidney		50% decrease in 24-hour urinary protein excretion in the absence of a reduction in eGFR ≥ 25% or an increase in serum creatinine ≥ 0.5 mg/dL
Liver		50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm

Abbreviations: IFE, immunofixation electrophoresis; dFLC, difference in concentration between involved and uninvolved free light chains; NT-pro BNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

*If a patient with AL amyloidosis caused by monoclonal λ light chain has a serum concentration of λ 254 mg/L and κ 24 mg/L, the dFLC is 230 mg/L.

†Reliable, widely available methods for defining peripheral and autonomic nervous system response were felt not to exist.[48]

The goals of therapy are prompt elimination of the misfolded amyloidogenic light chains, minimization of treatment toxicity, and support of the function of target organs. Virtually all patients with AL amyloidosis die because of heart failure or sudden death. Therefore, it is essential that hematologic response translates into stabilization or improvement of cardiac function to provide significant benefit in quality of life and survival. Table 2 reports the consensus criteria for hematologic and organ response,[47] recently updated at the 12th International Symposium on Amyloidosis.[48] Achieving a hematologic response translates into improved overall survival. Although partial responses can be beneficial,[49,50] it appears that significant reductions in free light chain levels are associated with the best clinical responses. For example, following treatment with high-dose intravenous melphalan supported with autologous hematopoietic SCT (HDM/SCT), reductions in FLC level of > 90% correlate with improved survival,[51] although the absolute level of FLC achieved after SCT therapy may also correlate.[44] Cardiac biomarkers demonstrate the link between hematologic and clinical responses. Pooled data on 300 patients from the centers in Pavia and London showed that in patients achieving a partial response following first-line treatment, the estimated 4-year overall survival was 52% for patients with an increase in NT-proBNP versus 88% for patients with a decrease ($P < .001$), and the latter was not significantly different from those who achieved complete response (CR). The cardiac biomarkers were more sensitive to functional changes than echocardiographic measurement of wall thickness.[52] These data support a new paradigm in the treatment of AL amyloidosis, in which both the underlying hematologic disorder and the end organ damage can be monitored with FLC and cardiac biomarkers to optimize therapy and minimize toxicity.

Alkylator Chemotherapy

Soon after the recognition that AL amyloidosis was caused by a clonal expansion of plasma cells, the type of chemotherapy used for multiple myeloma was examined for its efficacy in AL amyloidosis. This strategy continues to the present. It is essential to use clinical trials to gather data about efficacy and toxicity for patients with a low tumor burden of disease but impaired organ function.

The first effective regimen for multiple myeloma was melphalan chemotherapy combined with prednisone, and randomized studies demonstrated that this regimen had a survival benefit for patients with AL amyloidosis.[53,54] However, the rates of hematologic response to melphalan and prednisone were low and delayed, with a median time to response of 7 months (Table 3). Multidrug regimens containing vincristine, doxorubicin, and dexamethasone[69] or vincristine with multiple alkylator agents[70] were tested but failed to show convincing superiority over melphalan and prednisone.

More recently, dexamethasone has been substituted for prednisone in association with melphalan (MDex), and much higher hematologic response rates have been seen. A study of 46 patients ineligible for HDM/SCT reported a 67% hematologic response rate, including 33% CRs and organ responses in 48%, with severe adverse events in only 11% and two deaths during treatment.[61] All patients underwent Holter monitoring, and those with couplets or ventricular tachycardia received prophylactic amiodarone indefinitely. Median progression-free and overall survival were 3.8 and 5.1 years, respectively.[71] A prospective study of 159 patients ineligible for 200 mg/m^2 HDM/SCT who had been treated with MDex reported a hematologic response in 62% of patients, with 25% CRs and organ response in 35%.[72] Lower response rates were observed in cohorts that had a significant proportion of patients with severe cardiac involvement.[41,73]

A significant advance in myeloma chemotherapy was the use of HDM/SCT, and this approach has been adapted for patients with AL amyloidosis. The fragility of the amyloidosis patient population was soon evident, when series from some centers reported treatment-related mortality exceeding 40%[74] or more in those with cardiac involvement.[75] Nonetheless, some centers had more promising initial results that justified further trials.[76] A single-institutional study of 312 patients on sequential phase II trials reported a 40% CR rate in evaluable patients (23% by intention-to-treat) with treatment-related deaths in 13% and a median survival of 4.6 years.[59] In an attempt to reduce treatment-related toxicity, attenuated melphalan dosing has been used in high-risk and older patients, with reduced toxicity but generally with lower response rates.[59,60,77-79] Accumulating data indicate that benefits of HDM/SCT can be long-lasting. For 80 patients

Table 3. Available Treatments for AL Amyloidosis

Regimen	No. of Patients	No. of Patients Previously Treated	Patients With Heart Involvement (%)[a]	HemR/CR (%)	Organ Response (%)	TRM (%)	SAE Grade ≥ 3	Reference
Melphalan-prednisone-colchicine	50		76	NR	20	NR	8	Skinner et al[53]
Melphalan-prednisone	148[b]		NR[c]	28[d]	18	NR	5[e]	Kyle et al[54]
Dexamethasone	25[f]	13	39	NR	30	0	NR	Palladini et al[55]
Dexamethasone	25		68	40/16	12	8	NR	Gertz et al[56]
Dexamethasone	19	19	63	58/10	16	5	NR	Gertz et al[57]
Dexamethasone + maintenance IFN-α	87	14	50	33/15	45	7	51/67[g]	Dhodapkar et al[58]
HDM/SCT (single-center data)	312		45	59[h]/29	29	13	NR	Skinner et al[59]
HDM/SCT (single-center data)	171		49	68/NR	NR	12	NR	Gertz et al[60]
Melphalan-dexamethasone	46		70	67/35	48	4	11	Palladini et al[61]
Melphalan-dexamethasone	43		46	68/32	39	2	16	Jaccard et al[62]
Thalidomide-dexamethasone	31	31	38	48/19	26	0	65	Palladini et al[63]
Cyclophosphamide-thalidomide-dexamethasone	75	44	59	74/21	27	4	32	Wechalekar et al[64]
Lenalidomide ± dexamethasone	22	13	64	41/NR	23	18	86	Dispenzieri et al[65]
Lenalidomide ± dexamethasone	34	31	38	47/21	21	3	35	Sanchorawala et al[66]
Bortezomib	49	49	57	67/35	35	0	50/79[g]	Reece et al[67]
Bortezomib + dexamethasone	94[i]	76	73	71/25	30	0	29	Kastritis et al[42]
Pomalidomide + dexamethasone	25	25	80	47/10[k]	10	NR	56	Dispenzieri et al[68]

Abbreviations: AL, immunoglobin light chain amyloidosis; HemR, hematologic response; CR, complete response; TRM, treatment-related mortality; SAE, severe adverse event; NR, not reported; IFN-α, interferon alfa; HDM, high-dose melphalan; SCT, stem-cell transplantation.

[a]Criteria for heart involvement were heterogeneous before the adoption of the consensus criteria in 2005.[47]

[b]Including 71 patients treated with melphalan-prednisone-colchicine.

[c]Twenty percent of patients had dominant heart involvement.

[d]Composite response including, in addition to disappearance of or a reduction of at least 50% in the serum or urine monoclonal protein, an increase ≥ 1 g in serum albumin value, and a reduction ≥ 50% in urinary protein excretion.

[e]Includes development of myelodysplasia in seven patients and acute leukemia in one patient.

[f]Dose of 40 mg on days 1 to 4, every 21 days.

[g]Induction phase/maintenance phase.

[h]Reported as noncomplete hematologic response.

[i]Administration of bortezomib once weekly or twice weekly.

[j]Eleven percent of the patients did not receive dexamethasone.

[k]Very good partial responses.

followed for ≥ 10 years, the median survival was 57 months by intention-to-treat; in the 32 patients in this group who achieved a hematologic CR, the median survival was > 10 years.[80] Improvement in proteinuria and renal function occurred in 36%[81] to 60% of patients.[82] HDM/SCT is also associated with improvement in quality of life.[83]

Thus, excellent rates of hematologic responses can be seen with either oral melphalan and dexamethasone or HDM/SCT. Only a single randomized study[62] has addressed the question of which approach is more effective, and it failed to show a benefit for HDM/SCT. However, in this multicenter study, 26% of patients in the transplantation arm did not complete HDM/SCT, and the treatment-related mortality of patients who had transplantations was 24%. Thus, the question of which melphalan-containing regimen is superior remains uncertain.

New Agents Available in the Treatment of AL Amyloidosis

Thalidomide. Thalidomide as a single agent has limited efficacy and is poorly tolerated, with fatigue and sedation being the major dose-limiting toxicities followed by fluid retention, constipation, orthostasis, peripheral neuropathy, and worsening of renal function.[84] In another study of 31 patients treated with thalidomide in association with intermediate-dose dexamethasone,[63] 48% achieved hematologic responses, with 19% of patients achieving CRs and 26% having evidence of organ responses. However, treatment-related toxicity occurred in two thirds of patients, including symptomatic bradycardia in 26%. Thalidomide has been combined with melphalan and dexamethasone in 22 patients with advanced cardiac amyloidosis in an attempt to improve responses in this high-risk group, but only the subgroup of patients with preserved systolic function benefited from this combination.[85] Thalidomide has also been combined with cyclophosphamide and dexamethasone (CTD).[64] Thalidomide and dexamethasone dosing was risk-adapted for patients age > 70 years or for those with congestive heart failure or significant fluid overload, and the regimen was well-tolerated in this report.[64] A hematologic response was seen in 48 (74%) of 65 evaluable patients with CRs in 21%. The median progression-free survival was 32 months, and median survival from the start of therapy was 41 months. Toxicities included fluid retention, and treatment-related mortality was 4%. This regimen can be considered for stem-cell–sparing initial treatment.

Lenalidomide. Lenalidomide has been combined with dexamethasone in the treatment of AL. The most common adverse effects are cytopenia, rash, and fatigue. Both thalidomide and lenalidomide are prothrombotic, particularly in combination with corticosteroids. Doses of lenalidomide higher than 15 mg/d are poorly tolerated in patients with AL amyloidosis. Hematologic responses have ranged from 41% to 47%.[65,66]

Lenalidomide has been combined with melphalan and dexamethasone in newly diagnosed patients.[86] Hematologic responses were observed in 68% of patients, and organ responses were observed in 50%. Lenalidomide has also been combined with cyclophosphamide and dexamethasone.[87] The overall hematologic response rate in 35 patients was 60%, and in those receiving at least four cycles, the response rate was 87%. The median overall survival was 16.1 months. All six patients who died had significant cardiac involvement. Other groups have had similar experience with this combination.[88,89]

Pomalidomide. The immunomodulator pomalidomide was administered along with dexamethasone to 25 patients enrolled over a 12-month period.[68] All patients had previously received alkylating agents, including prior ASTC in 12, prior lenalidomide or thalidomide in 13, and prior bortezomib in 10. The hematologic response rate in evaluable patients was 47%, which warrants further investigation of this combination.

Bortezomib. By inhibiting proteasome function in plasma cells, bortezomib triggers stress-activated protein kinases and mitochondrial apoptotic signaling. Amyloidogenic plasma cells that synthesize misfolded light chains with consequent overload of the ubiquitin-proteasome system may be particularly vulnerable to proteasome inhibition.[90,91] In the first study of the efficacy of bortezomib in association with dexamethasone,[92] 94% of evaluable patients had a hematologic response, including patients who had relapsed or were refractory to other therapies. The National Amyloidosis Center in Britain reported on 20 relapsed or refractory patients treated with bortezomib.[93] A hematologic response was seen in 80% of patients, 15% achieved CRs, and 30% had organ responses. In a multicenter phase I/II dose-escalation study of bortezomib,[94] hematologic responses occurred in 50% of 30 evaluable pretreated patients with 20% CRs, and there were no treatment-related deaths. The median time to response was only 1.2 months, and the once-weekly bortezomib regimen was associated with lower neurotoxicity. The results of the phase II study[67] are reported in Table 3. Data from three international centers on 94 (18 previously untreated) patients treated with bortezomib with or without dexamethasone found a hematologic response in 71% with 25% CRs (47% CRs in previously untreated patients). Notably, a cardiac response was documented in 29% of patients, and the 1-year survival rate was 76%. Baseline NT-proBNP was independently associated with survival. The most common nonhematologic toxicities were fatigue, peripheral sensory neuropathy, exacerbation of orthostatic hypotension, peripheral edema, and constipation or diarrhea.[42] Bortezomib and dexamethasone have also been used following risk-adapted melphalan and SCT to improve the depth of response.[95] Seventeen of 23 patients with transplantations received adjuvant post-transplantation bortezomib and dexamethasone, 74% achieved a CR, and 58% had organ responses. Combining bortezomib with melphalan or cyclophosphamide in small series of patients has yielded hematologic response rates of 94% and 100%, respectively.[96,97] Thus, bortezomib is rapidly active in AL amyloidosis with high rates of hematologic and organ responses.

Choice of Therapy

Early diagnosis is essential since it allows a broader range of therapeutic options. Treatment for AL amyloidosis is highly individualized and is based on age, organ dysfunction, and regimen toxicities. The algorithm of Figure 3 presents the standard of care at our centers. The usual eligibility criteria for HDM/SCT at 200 mg/m^2 include

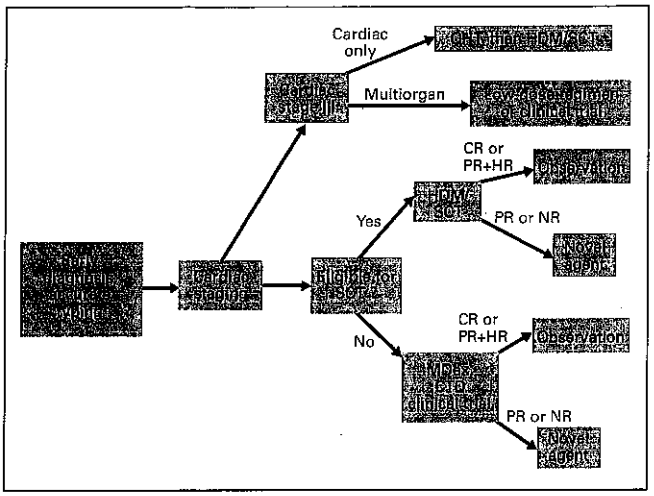

Fig 3. Treatment algorithm for immunoglobin light chain amyloidosis. Patients who present with advanced cardiac disease may not tolerate high-dose corticosteroids or multidrug regimens. If they have isolated cardiac disease, orthotopic heart transplantation (OHT) should be considered, followed by high-dose intravenous melphalan supported with stem-cell transplantation (HDM/SCT) to prevent amyloid deposition in the transplanted heart. If the patient is not a transplant candidate, a low-dose regimen (low-dose melphalan plus dexamethasone plus low-dose bortezomib, or melphalan-prednisone plus low-dose thalidomide), should be considered. Patients younger than 65 years with adequate organ function may be considered for HDM/SCT at 200 mg/m^2. Melphalan-dexamethasone (MDex) or thalidomide-cyclophosphamide-dexamethasone (CTD) are reasonable alternatives, particularly for patients at higher risk of toxicity with HDM/SCT. Patients achieving complete response (CR) or partial response (PR) associated with stabilization or reduction of cardiac biomarkers (heart response [HR]) may stop treatment and start close follow-up. Patients who obtain partial response without HR and those with no response (NR) should be treated with novel agents, alone or in combination. Because data from clinical trials are maturing, the combination of novel agents with alkylators may move to the forefront.

age ≤ 65 years, normal cardiac troponin concentration, left ventricular ejection fraction ≥ 45%, systolic blood pressure ≥ 90 mmHg, diffusion lung capacity for carbon monoxide > 50%, performance status 0 to 2, and creatinine clearance > 50 mL/min. Clinical trials are needed to determine the relative efficacy of reduced-intensity (100 to 150 mg/m^2) HDM/SCT, MDex, or CTD. If HDM/SCT at 200 mg/m^2 cannot be instituted promptly, it may be preceded by stem-cell–sparing regimens such as CTD or bortezomib-dexamethasone.

The choice of novel agent depends on organ function and pace of disease. Although bortezomib acts quickly to reduce light chain levels, it can exacerbate neuropathy and cardiac symptoms; less frequent (weekly) and/or reduced dosing (1 to 1.3 mg/m^2 weekly or 0.7 to 1 mg/m^2 twice weekly) should be used in patients with involvement of these systems. Thalidomide can also cause neuropathy, and thalidomide and lenalidomide have been associated with thromboembolism and worsening of renal function, which should be monitored closely during treatment.[84,98] Pomalidomide has shown activity in heavily pretreated relapsed or refractory patients.

The combinations of lenalidomide[86-89] and bortezomib[96,97] with alkylators melphalan and cyclophosphamide have been tested in small series of patients with promising results, and controlled studies are warranted. A multinational study comparing melphalan and dexamethasone to melphalan, dexamethasone, and bortezomib is scheduled to begin in 2011.

Close monitoring of clonal response, evaluated by FLC assay, and of cardiac response, evaluated by NT-proBNP or BNP, should be

performed regularly to guide regimen changes and duration of therapy. Whenever possible, patients should be treated within controlled clinical trials.

Supportive Care

Caution is required in the use of standard heart failure medications in patients with amyloidosis. Digoxin and calcium channel blockers have been associated with excess toxicity. Angiotensin-converting enzyme inhibitors can promote hypotension in AL amyloidosis and should generally be avoided. Prophylactic amiodarone (200 mg/d 5 days/wk, continued indefinitely) has been incorporated into therapy trials of amyloidosis to reduce the risk of sudden cardiac death if complex ventricular arrhythmias are detected on Holter ECG.[61] The use of beta blockers in patients with cardiac amyloid is associated with a higher mortality rate.[99] Diuretics are the mainstay of therapy to manage edema, but patients with cardiac amyloidosis have restrictive hemodynamics and often require high filling pressures to maintain adequate cardiac output. Attempts to reduce edema often will lower the filling pressure to the point that significant drops in cardiac output with resultant syncope and reduced renal blood flow can occur. Alpha agonists such as midodrine can improve orthostatic hypotension due to autonomic neuropathy. Implantable cardiac defibrillators have been used in patients with cardiac involvement because of the high incidence of sudden death, but strong evidence demonstrating their efficacy in this disease is lacking.[100] Both cardiac[101,102] and renal transplantation[103] have been successfully carried out in AL amyloidosis. Positive outcomes require strict control of precursor protein production or disease recurrence in the transplanted organ is inevitable.

CONCLUSIONS AND PERSPECTIVES

To date, treatment of AL amyloidosis has exploited the advances made in the chemotherapy of multiple myeloma being directed at the suppression of the amyloidogenic plasma cell clone. In at least one third of patients, the clone exhibits unique sensitivity to new chemotherapeutic combinations, increasing the fraction of patients who achieve deep and durable responses. FLC, troponin, NT-proBNP, and BNP biomarkers guide selection and duration of therapy. Treatments will continue to be refined, but the key remains early diagnosis before end-stage organ failure has occurred.

Advances in the understanding of the molecular mechanisms involved in amyloid formation and tissue damage, summarized in Figure 1, have revealed several new drug targets and therapeutic approaches. As indicated by the callout arrows in Figure 1, there are several potential opportunities to counter the amyloid process: (A) The synthesis of the amyloidogenic precursor may be eliminated by using chemotherapy in AL amyloidosis or liver transplantation in ATTR amyloidosis; silencing by using RNA interference is being tested in animal models. (B) Inhibitors of proteases (secretase) and metal protein attenuating compounds are being evaluated in trials. (C) Compounds that interfere with the binding of glycosaminoglycans to the amyloid proteins (eprodisate) have been successful in secondary amyloidosis.[2] (D) Small molecules capable of stabilizing the amyloid precursor and preventing its misfolding and aggregation (diflunisal, tafamidis)[3] are being tested in ATTR amyloidosis. (E) SAP can be cleared from amyloid deposits by using small palindromic drugs (eg, CPHPC).[4] (F) The clearance of amyloid deposits can be promoted and accelerated by specific antibodies through passive[5] and active immunotherapy,[6] or by combining CPHPC with anti-SAP antibodies.[7] In the next few years, exploitation of these approaches is likely to yield effective new therapies. Ultimately, amyloid diseases will be treated with combination cytotoxic, targeted, and immunologic approaches that reduce protein precursor production, prevent aggregation, and induce fibril resorption.

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