How We Treat Systemic Light-Chain Amyloidosis

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Abstract: Systemic light-chain (AL) amyloidosis is a multisystem disease characterized by organ toxicity and damage due to monoclonal free light chains, which are produced by a neoplastic clone of plasma cells in bone marrow. Current treatment strategies target the clone in order to decrease the production of the pathologic light chains and thereby stop or reverse organ toxicity and damage. AL amyloidosis remains a formidable and often incurable disease despite treatment options that include corticosteroids, cytotoxic chemotherapy, risk-adapted melphalan, autologous hematopoietic stem cell transplantation, proteasome inhibitors, and immunomodulatory drugs. New and effective treatment approaches that can reverse the organ damage are urgently needed. Physicians and clinical staff should be aware of the importance of providing best supportive care to patients with advanced AL-related organ dysfunction, given the patients' often tenuous hemodynamics and fragile functional status. Organ transplantation has a role in selected clinical situations, and the treating hematologist should be aware of this sometimes-useful option.

Keywords
Amyloidosis, biomarkers, monoclonal gammopathy, novel agents, stem cell transplantation

Introduction

Systemic light-chain (AL) amyloidosis is a rare and often fatal disease caused by toxic immunoglobulin molecules—usually light chains—and the extracellular fibrillar deposits they form, which cause progressive dysfunction of vital organs and eventually death, mainly from cardiac causes.[1,2] Amyloidosis is diagnosed by Congo red staining of a tissue biopsy specimen, which shows pathognomonic apple-green dichroism under polarized light.[3]

More generally, amyloid fibrils are derived from precursor proteins such as light chains that self-assemble and deposit in organs, causing organ dysfunction. The fibrils have a characteristic β-pleated secondary structure, seen through electron microscopy as 8- to 10-nm linear nonbranching fibrils.[4] AL amyloidosis is caused by monoclonal immunoglobulin light chains produced by a neoplastic clone of plasma cells in the bone marrow (Table 1).[5]

A recent case-control study has clearly shown that increased serum levels of free light chain (FLC) can precede the clinical diagnosis of

Table 1. The Major Amyloidosis Subtypes

Precursor Protein	Amyloid Type	Clinical Presentation/ Involvement
Monoclonal immunoglobulin light chain	AL	Localized or systemic (heart, kidney, GI tract, liver, peripheral nerves, soft tissue)
Monoclonal immunoglobulin heavy chain	AH	Localized or systemic (heart, kidney, GI tract, liver, peripheral nerves, soft tissue)
Serum amyloid A (SAA)	AA	Renal (most common), liver, GI tract, autonomic nervous system
TTR wild-type (senile systemic)	Wild-type ATTR	Heart, soft tissue
TTR mutant[a]	Mutant ATTR	Hereditary peripheral or autonomic neuropathy, cardiomyopathy, vitreous opacities
LECT2	ALect2	Hepatic and renal; in Hispanic populations and those with preexisting liver disease (eg, hepatitis C)
β_2-microglobulin	Aβ_2M	Triad of carpal tunnel syndrome, shoulder pain, and flexor tenosynovitis of hands in long-term dialysis patients
Fibrinogen Aα-chain[a]	AFib	Visceral (mainly renal, also liver, spleen)
Gelsolin[a]	AGel	Cranial nerves and cornea
Lysozyme[a]	ALys	Visceral (mainly renal, also liver, spleen, lung, GI)

AA, AA amyloidosis; Aβ_2M, β_2-microglobulin amyloidosis; AFib, fibrinogen Aα-chain amyloidosis; AGel, gelsolin amyloidosis; AH, heavy-chain amyloidosis; AL, light-chain amyloidosis; ALect2, LECT2-associated amyloidosis; ALys, lysozyme amyloidosis; ATTR, transthyretin amyloidosis; GI, gastrointestinal; LECT2, leukocyte cell–derived chemotaxin 2; TTR, transthyretin.

[a] Hereditary amyloidosis.

AL amyloidosis by more than a decade.[5,6] This observation suggests that the organ toxicity of pathologic light chains is cumulative, and that the neoplastic plasma cell clone is active for years prior to the clinical signs and symptoms. Even in patients with preexisting plasma cell dyscrasias who are under clinical vigilance,[7] timely diagnosis of AL amyloidosis remains a challenge. Thus, heightened clinical suspicion is needed to detect AL amyloidosis before organ function is compromised, particularly in patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma (SMM), active myeloma, and lymphoplasmacytic lymphoma.

MGUS and SMM patients with elevated FLCs are at risk for developing AL amyloidosis. As a result, tracking FLC, albuminuria, and cardiac biomarkers at annual intervals is useful.[8] N-terminal brain-type natriuretic peptide (NT-proBNP) and cardiac troponins T and I are sensitive biomarkers that can assist in early detection of cardiac involvement during the natural history of AL amyloidosis. NT-proBNP is also useful to monitor disease progression and to gauge response to therapy. Recently, a study found that elevated von Willebrand factor (vWF) antigen levels were associated with a high risk of early death and shorter survival in patients with AL amyloidosis, independent of cardiac biomarkers.[9] However, before vWF antigen can be used as a biomarker in AL amyloidosis, further prospective validation is necessary.

Amyloidosis should be suspected in certain clinical settings, including nephrotic syndrome with albuminuria rather than Bence Jones proteinuria, peripheral or autonomic neuropathy, diastolic heart failure with normal- or low-voltage electrocardiogram (ECG) (particularly in patients with historical hypertension who no longer require antihypertensive medications), left ventricular hypertrophy in patients without history of hypertension, and recurrent or bilateral carpal tunnel syndrome.

How to Evaluate a Patient With Systemic AL Amyloidosis

The most common organs affected by AL amyloidosis at the time of presentation are the heart (50%), kidneys (50%), liver and gastrointestinal tract (25%), and peripheral nerves (20%) (Table 2).[10] The involvement of multiple organs is common at the time of diagnosis; therefore, a thorough assessment must be performed, including a detailed history and physical examination, laboratory studies, and cardiovascular imaging studies. Abdominal fat aspiration and staining with Congo red is a simple, high-yield method available in the office to obtain tissue for diagnosis. A fat aspirate that is negative for amyloid does not exclude amyloidosis. A biopsy of involved organ, rectum, or labial salivary gland can be considered when abdominal fat pad is negative for amyloid but amyloidosis remains a plausible diagnosis.[11] Biopsy of the symptomatic organ has the highest diagnostic yield with a minimally increased risk of bleeding in certain cases.[12] Finding amyloid in a bone marrow biopsy with a clonal population of plasma cells does not establish the diagnosis of AL amyloidosis; marrow core biopsies in AL amyloidosis patients contain amyloid in approximately 50% of cases.[13]

Immunoglobulin light chains are not the only proteins that can cause systemic amyloidosis. Other types of amyloid-forming proteins include the thyroxine and vitamin A binding protein transthyretin (TTR) in both mutant and wild-type forms, serum amyloid A (SAA), and mutant forms of fibrinogen, apolipoprotein A1,

Table 2. Stepwise Evaluation and Staging of an Amyloid Patient

Establish diagnosis by tissue staining with Congo red
- Aspiration of abdominal fat
- Biopsy of an involved organ
Rule out monoclonal gammopathy
- SPEP and serum IFE
- Serum FLC
- Urine PEP and IFE
- Bone marrow aspiration and biopsy:
(a) staining for κ and λ light chains and Congo red staining
(b) cytogenetics and FISH of CD138-selected plasma cells
Type amyloid to identify the precursor protein
- Laser microdissection by mass spectrometry (when indicated)
Clinical staging of disease
- Cardiac: ECG, ECHO, NT-proBNP, Troponin (T or I)
- Renal: 24-hour urine protein, estimated GFR
- Gastrointestinal: EGD or colonoscopy and biopsy (if indicated)
- Liver: alkaline phosphatase >1.5 times upper limit of normal indicates involvement
- Peripheral and autonomic nervous system: orthostatic vital signs, EMG testing
- Skeletal survey or spinal and pelvic MRI if myeloma-related organ damage is suspected

ECHO, echocardiogram; EGD, esophagogastroduodenoscopy; ECG, electrocardiogram; EMG, electromyography; FISH, fluorescence in situ hybridization; FLC, free light chain; GFR, glomerular filtration rate; IFE, immunofixation; MRI, magnetic resonance imaging; NTpro-BNP, N-terminal brain-type natriuretic peptide; PEP, protein electrophoresis; SPEP, serum protein electrophoresis.

β_2-microglobulin, gelsolin, and lysozyme (Table 1). Recently, mass spectrometry–based proteomics has led to the discovery of a new amyloid-forming protein, leukocyte cell–derived chemotaxin 2 (LECT2). This protein can cause hepatic and renal amyloidosis in Hispanic patients, patients with chronic active hepatitis C, and patients with other preexisting hepatic conditions, such as steatohepatitis.[14,15]

By convention, the various types of systemic amyloidosis are denoted by the letter *A* before the protein name; for example, ATTR is the designation for both hereditary and age-related TTR amyloid types. Hereditary types of systemic amyloidosis can present de novo; the most common hereditary form, the V122I ATTR variant, is associated with an aberrant gene present in 3.9% of blacks in the United States and 5% in West Africa. More than 100 mutant TTR variants have been identified worldwide as causes of hereditary amyloidosis, the vast majority being rare. The TTR protein is a tetramer, and mutant variants enhance dissociation and monomer misfolding that result in fibril formation and aggregation over decades. Although mutant variants of TTR cause hereditary amyloidosis, age-related (or senile) ATTR is due to wild-type TTR that has been affected in an unknown way to produce systemic amyloidosis, most often as cardiac amyloid involvement in elderly men. By some estimates, the number of individuals with age-related ATTR in the United States exceeds several million; however, the natural history of the disease and the scope of its morbidity are not well described.

AL amyloidosis due to immunoglobulin light chains can evolve from a prior or newly diagnosed monoclonal gammopathy (MG); however, in certain categories of patients, 2 possible precursor proteins (AL and non-AL) may coexist. Therefore, the protein responsible for amyloid-related organ damage should be determined before extensive treatment in order to minimize needless toxicity during therapy. In such cases, laser microdissection and mass spectrometry of proteins in the amyloid tissue deposits are used for amyloid typing (ie, for specifically identifying the culprit protein).[16,17] Mass spectrometry–based amyloid typing is required for many groups of patients, including those with MG and cardiac involvement who are older than 70 years of age and may have age-related ATTR; blacks with amyloidosis and MG who may have mutant hereditary ATTR amyloid; patients with MG and inflammatory disorders such as severe gout or inflammatory bowel disease (disorders that can cause serum amyloid A [SAA amyloid protein], causing AA amyloidosis; and Hispanics or other patients with chronic hepatitis C and MG who may have hepatic and/or renal amyloid due to ALect2. Mass spectrometry–based amyloid typing remains the gold standard for amyloid typing when 2 amyloid-forming precursor proteins are suspected.[16,17] Although both ATTR and AL amyloidosis can cause cardiomyopathy and heart failure, AL amyloidosis progresses much faster.[18] Thus, survival depends on timely diagnosis and prompt intervention. Amyloidosis caused by SAA is predominantly extracardiac, with renal amyloidosis as the most common manifestation.[18,19]

The approach to the clinical evaluation for systemic involvement is summarized in Table 2. The ECG hallmark of low voltage (found in 45%-70% of patients) usually indicates more advanced cardiac involvement.[20] An echocardiogram (ECHO) including the measurement of ventricular wall thickness and assessment of diastolic parameters is essential. It is important to note that up to one-third of patients with AL cardiac amyloidosis can have normal left ventricular wall thickness (<12 mm).[21] Thus, absence of left ventricular hypertrophy does not rule out cardiac amyloidosis. The NT-proBNP and cardiac troponins (T and I) are highly sensitive biomarkers for myocardial involvement, and the level of the NT-proBNP can be elevated well before structural or functional changes are recognized by ECHO or ECG. Cardiac magnetic resonance imaging (MRI) can

show widespread subendocardial enhancement, representing infiltration with amyloid protein. Cardiac MRIs can complement ECHO findings, particularly in patients who have normal ventricular wall thickness in the ECHO; however, gadolinium is contraindicated in patients with moderate or severe renal dysfunction, which is not uncommon in this patient population. In patients at risk for cardiac AL (eg, an MGUS patient with new unexplained dyspnea on exertion, unrevealing ECHO results, and "clean coronaries" on an angiogram), cardiac biomarker screening is indicated, although a definitive diagnosis requires tissue biopsy. The NT-proBNP and cardiac troponin (T or I) cardiac staging system has been useful both in the clinic and in clinical trials.[22,23] Median survivals for cardiac stages I, II, and III are 26.4, 10.5, and 3.5 months, respectively. Increasing levels of these biomarkers often indicate disease progression, with 2 possible exceptions: (1) elevated biomarker levels can be seen in patients with renal insufficiency, because biomarker clearance depends on the glomerular filtration rate[24] and (2) immunomodulatory (IMiD) therapy, most notably with lenalidomide (Revlimid, Celgene), has been associated with increasing levels of cardiac biomarkers and apparent potential for cardiotoxicity, through an undefined mechanism.[25,26] Lenalidomide has also been linked to azotemia and renal failure (including end-stage renal disease) in patients with AL amyloidosis.[27]

Renal involvement is assessed by quantification of proteinuria in a 24-hour urine collection, measurement of creatinine clearance, evaluation of urine protein electrophoresis, and immunofixation for a monoclonal protein.[10,18,19] The serum FLC assay is an important advancement, because it can be used as a diagnostic tool and as a biomarker test to monitor disease activity, assess the response to therapy, and determine prognosis.[18,23] The elevated serum FLC is usually the pathogenic amyloid precursor protein, and declining levels of FLC after therapy are associated with improved survival, particularly in patients with complete response and very good partial response (VGPR; Table 3). There is no established role for urine FLC studies.

Essential to the initial evaluation, bone marrow aspiration and biopsy are used for: (1) Congo red staining to test amyloid levels, (2) immunohistochemical staining for κ and λ light chains (λ light chains are 4 times as frequent as κ light chains), and (3) staining for CD138 to estimate the size of the plasma cell clone (≤10% in approximately 60% of cases).[8] The genetic endowment of the clonal plasma cells is important and may predict the biological behavior of the clone, including its susceptibility to therapy.[28,29] Bone marrow aspirate should be sent for karyotyping and fluorescence in situ hybridization to test for the chromosomal aberrations t(11;14), gain 1q, t(14;16), t(4;14), del 13q, and del 17p.[28-31] The aberration t(11;14) with overexpression of *CCND1* and gain of 1q have been identified as important prognostic factors relevant to the response to therapy. The translocation t(11;14) is found in almost 60% of patients and is associated with higher complete response rates to melphalan-based therapy, whereas gain 1q occurs in almost 25% of patients and is associated with lower response rates to melphalan-based therapies.[32] Del 17p and t(14;16) are uncommon and may suggest higher clonal proliferation and shorter remission durations.[30]

Table 3. Validated Criteria for Evaluation of Response and Progression in AL Amyloidosis

Hematologic Response Criteria
CR: negative serum and urine IFE, normal FLC levels and ratio
VGPR: reduction of dFLC to <40 mg/L
PR: >50% reduction in the dFLC
No response: less than a PR
Progression is defined as any one of the following: (a) from a CR, any detectable monoclonal protein or abnormal FLC ratio (light chain must double), (b) from a PR, 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M protein to >200 mg/day (a visible peak must be present), or FLC increase of 50% to >100 mg/L
Cardiac Response Criteria
Response: (a) NT-proBNP response (>30% and >300 ng/L decrease in patients with baseline NT-proBNP ≥650 ng/L) or (b) NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4)
Progression: (a) NT-proBNP progression (>30% and >300 ng/L increase)[a] or cTn progression (≥33% increase) or (b) ejection fraction progression (≥10% decrease)
Renal Response Criteria
Response: decrease in proteinuria by ≥30% or <0.5 g/24 hours in the absence of renal progression
Progression: decrease in GFR by >25% at 6 months

CR, complete response; cTn, cardiac troponin; dFLC, difference between involved and uninvolved free light chain levels; FLC, free light chain; GFR, glomerular filtration rate; IFE, immunofixation; NT-proBNP, N-terminal brain-type natriuretic peptide; NYHA, New York Heart Association; PR, partial response; VGPR, very good partial response.

[a] Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.

How to Treat a Newly Diagnosed Patient With Systemic AL Amyloidosis

Although AL amyloidosis remains an often incurable disease, much progress has been made in the last 25 years, and important aspects of clinical care for AL amyloidosis patients are guided by evidence-based treatment recommendations. Consensus criteria have been developed and validated for organ involvement, cardiac and renal staging, and hematologic, cardiac, and renal responses.

These criteria are widely used in both the clinical and research settings (Table 3).[22,23,33] Hematologic and cardiac responses are associated with prolonged survival, and renal responses are associated with longer renal survival (ie, freedom from progression to end-stage renal disease leading to hemodialysis).[32] Stopping production of the pathologic FLC translates into significant benefit for most patients, excluding those with advanced cardiac or renal dysfunction.[22,32-34]

From Colchicine to Autologous Hematopoietic Stem Cell Transplantation

The goal of therapy in AL amyloidosis is to curb the continued production of pathologic immunoglobulin FLCs by eliminating the underlying neoplastic plasma cell clone that produces them. The overall aims of the treatment are to achieve a sustained VGPR or complete hematologic response and to improve organ function, thereby prolonging overall survival. Decades ago, the antimitotic agent and microtubule polymerization inhibitor colchicine was used to treat AL amyloidosis because of its utility in reactive AA amyloidosis in familial Mediterranean fever.[35] However, subsequent studies confirmed the inactivity of colchicine.[36-37] More recently, therapies for AL amyloidosis have largely been modeled on those used to treat the plasma cell neoplasm multiple myeloma. Although only a minority of AL amyloidosis patients later develop myeloma, 10% to 15% of patients with myeloma have or develop AL amyloidosis organ disease. In an important single-center clinical trial using oral melphalan and prednisone (MP)—the traditional 20th-century therapy for myeloma—patients with AL amyloidosis who received MP with or without colchicine had improved overall survival compared with the colchicine-alone group, albeit with a median survival of 18 vs 8 months, respectively (see Figure 1 online at www.hematologyandoncology.net).[37]

In the late 20th century, melphalan-based therapies dominated the treatment landscape, and high-dose intravenous melphalan followed by autologous hematopoietic stem cell transplantation (SCT) took center stage for eligible patients. These new treatments demonstrated high rates of hematologic remission, reversal of organ dysfunction, and survival benefit without the risks of myelodysplasia and secondary acute myelogenous leukemia typically associated with oral melphalan-based therapies.[39,40]

Although these gains were encouraging, SCT in this era was associated with unacceptably high procedure-related mortality, particularly in patients with cardiac involvement.[39] This led to the era of risk-adapted melphalan dosing with SCT, a novel concept in which the dose of intravenous melphalan was attenuated based on age and organ involvement in order to reduce the treatment-related mortality. Using this system, melphalan was dosed from 100 to 200 mg/m^2 based on age, renal function, and cardiac involvement. This approach, with refined patient selection and treatment criteria, reduced treatment-related mortality to less than 5% in high-volume centers.[41,42] Risk-adapted melphalan with SCT has redefined the role of SCT as a safe and effective procedure for AL amyloidosis patients, although only 30% of patients are currently eligible for this approach at diagnosis.

By the turn of the century, it was obvious that SCT patients who achieved a complete hematologic response had improved overall survival compared with those who did not (see Figure 2 online at www.hematologyandoncology.net).[43] At this time, complete hematologic response was scored by serum and urine immunofixation and marrow-based criteria, because the FLC assay was not yet in clinical use. The benefit of achieving a complete hematologic response with SCT was confirmed by a large single-center retrospective analysis just over a decade later (see Figure 3 online at www.hematologyandoncology.net).[44] The complete response rate (immunofixation-based) with SCT is approximately 35%, and those with a complete response have a longer overall survival than those without (13.2 vs 5.9 years, respectively).[44] It was also clear that risk-adapted melphalan dosing at 140 mg/m^2 or less was associated with a lower complete response rate than melphalan at 200 mg/m^2, setting the stage for post-SCT consolidation studies.

Though never directly compared in clinical trials with MP, oral melphalan and dexamethasone (MDex) became the standard first-line therapy for patients not eligible for SCT. In historical comparisons with MP, MDex has been shown to achieve higher hematologic (20% vs 67%, respectively) and organ (18% vs 48%, respectively) response rates and markedly improved median overall survival (1.5 vs >4 years, respectively) (see Figure 4 online at www.hematologyandoncology.net).[45] MDex was directly compared with SCT, however, in a notable multicenter phase 3 trial performed by the Myeloma Autotransplant Group in France.[46] Two limitations of this study likely influenced outcomes in the SCT arm: (1) the patient selection and treatment criteria used in the United States by that time were not employed in the trial, and (2) many centers had little experience with SCT for AL. Nevertheless, the results of this trial (see Figure 5 online at www.hematologyandoncology.net), and particularly the benefits confirmed for MDex treatment, led to the adoption of MDex as standard therapy for AL amyloidosis in Europe.

Era of Bortezomib

Since the era of colchicine, much progress has been made in the quest for an ideal therapy in AL. The most remarkable of the novel agents is bortezomib (Velcade, Millennium Pharmaceuticals), the first-in-class drug

that established proteasome inhibition as an effective therapy to target clonal plasma cell diseases. When used after risk-adapted melphalan with SCT, bortezomib-based therapy can complement and consolidate the gain achieved by SCT, particularly in those who do not attain a complete response with SCT. Using this approach, 1-year complete response rates of more than 60% can be achieved (tested with the modern immunofixation- and FLC-based response criteria) (see Figure 6 online at www.hematologyandoncology.net).[47] Modern combination therapies based on the backbone of bortezomib—such as cyclophosphamide, bortezomib, and dexamethasone (CyBorD or VCD)—are in widespread clinical use with response rates that are strikingly high.[47-49] However, the durability of such responses is unclear at this time owing to limited follow-up.

It appears that bortezomib is able to change the natural history of AL amyloidosis because of the frequent, prompt, and sustained short-term reduction in FLCs. CyBorD is often used in SCT-eligible patients as induction therapy, pending insurance approval. Bortezomib-based regimens are also used as consolidation after SCT, as noted above.[47] Bortezomib-based therapy has the potential to reverse organ damage and enable an initially SCT-ineligible patient to become SCT eligible after induction, in which case SCT becomes the consolidative choice.[48-50] Prospective clinical trials are needed to determine the value of all of these approaches. As more effective and less toxic therapies become available, the role, timing, and sequencing of SCT in the overall treatment strategy of AL amyloidosis will undergo further redefinition. The new proteasome inhibitors currently in clinical trials will also likely increase the treatment options for AL amyloidosis patients, and the ongoing European phase 3 trial comparing MDex—the standard therapy—with the combination of bortezomib and MDex for newly diagnosed AL amyloidosis patients may alter the landscape for initial therapy in Europe (EudraCT Number: 2010-022395-31).

Treatment of Newly Diagnosed High-Risk Patients With AL Amyloidosis

Patients with stage III cardiac disease are at high risk of death, mostly occurring within the first few months after the diagnosis. Though there has been no direct comparison in clinical trials, CyBorD is rapidly replacing MDex as the standard of care in transplant-ineligible patients and in newly diagnosed patients with stage III cardiac involvement (see Figure 7A online at www.hematologyandoncology.net).[51,52] In newly diagnosed patients with stage III (both elevated troponin and NT-proBNP) cardiac involvement treated at multiple centers, the survival of patients with NT-proBNP levels less than 9500 ng/mL was markedly better than that of patients whose levels exceeded that threshold (see Figure 7B online at www.hematologyandoncology.net).[51,52] When such patients cannot tolerate bortezomib or become resistant to it, there remains a dearth of therapies that can rapidly decrease the levels of FLC and rescue the myocytes from ongoing proteotoxicity.

Therapies that inhibit amyloid formation and enhance resorption by targeting circulating amyloidogenic FLC and fibrillar deposits are in clinical trials now. The first of these, the monoclonal antibody NEOD001, is currently in a clinical phase 1/2 trial (NCT01707264). Initial results suggest that the drug is safe, and possibly advantageous to patients with elevated NT-proBNP.[53] This agent may hold promise for newly diagnosed patients with advanced cardiac involvement, and a phase 3 trial in that study population will soon begin (NCT02312206).

Treatment of Relapsed or Refractory Patients With AL Amyloidosis

Relapsed or refractory patients who are naive to bortezomib should be treated with a bortezomib-containing combination therapy. This was demonstrated in an update from the CAN2007 phase 1/2 trial, which found that single-agent bortezomib produced durable hematologic responses and promising long-term overall survival in relapsed AL amyloidosis patients who were previously exposed to MDex, lenalidomide, or thalidomide and SCT.[54] Though the efficacy was similar (65% hematologic response rates), a once-weekly bortezomib schedule was better tolerated than a twice-weekly schedule. A novel finding of this update is that the hematologic response achieved by single-agent bortezomib was sustained for 1 year or longer in 80% of patients.

New proteasome inhibitors—notably carfilzomib (Kyprolis, Onyx) and ixazomib (MLN9708)—are in clinical trials for AL. Carfilzomib, an irreversible inhibitor of the proteasome, is US Food and Drug Administration (FDA)–approved for myeloma patients refractory to both bortezomib and an IMiD agent (lenalidomide or thalidomide). Given intravenously, carfilzomib is currently in a phase 1 clinical trial for previously treated AL amyloidosis patients (NCT01789242). The attraction for carfilzomib in AL amyloidosis comes from the fact that it carries a lower risk of peripheral neuropathy and does not have cumulative bone marrow suppressive effects; however, given the relatively high overall number of cardiac events (21%) and cardiac failure (7.2%) in patients with multiple myeloma treated with carfilzomib, the tolerability of this agent in patients with AL amyloidosis and advanced cardiac involvement remains an area of concern.[55,56] Once completed, the phase 1/2 trial will help to address this concern, and further studies are anticipated.

Ixazomib, the first oral proteasome inhibitor to be tested in patients with AL, was shown to be safe and effective in a phase 1 trial (NCT01318902) in previously

treated patients with AL. The drug is now being used with oral dexamethasone in a global phase 3 registration trial for that population of AL amyloidosis patients (NCT01659658). Ixazomib is a potent, reversible, and specific 20S proteasome inhibitor; its long half-life allows the agent to be administered at effective doses weekly 3 times a month.[57-59] A recently reported phase 1 trial of weekly oral ixazomib in heavily pretreated myeloma patients with prior exposure to IMiD drugs and bortezomib showed that it was well tolerated with infrequent (10%) and less severe (all grade 1 or 2) peripheral neuropathy.[58] Another phase 1/2 study of weekly oral ixazomib in combination with lenalidomide and dexamethasone in previously untreated patients with myeloma showed that grade 3 or 4 neuropathy was seen in less than 5% of patients.[59]

Both the phase 1 data in AL amyloidosis and these results in myeloma provided the basis for the current global phase 3 trial of ixazomib with dexamethasone vs physician's choice for patients with relapsed or refractory systemic AL amyloidosis. The physician's choice of treatment is selected by the treating investigator from a prespecified list of regimens available in clinical practice, such as dexamethasone alone, dexamethasone plus an alkylating agent (melphalan or cyclophosphamide), or dexamethasone plus an IMiD (thalidomide or lenalidomide). Crossover to the investigational treatment arm is not permitted. This study is an excellent example of the kind of multinational and multicenter collaborative effort needed in order to evaluate new therapies for this uncommon and devastating disease. We hope to see more studies of proteasome inhibitors combined with new agents (eg, monoclonal antibodies) in future years, thereby providing more effective options for patients with AL.

Immunomodulatory Drugs: Thalidomide, Lenalidomide, and Pomalidomide

The IMiDs thalidomide, lenalidomide, and pomalidomide (Pomalyst, Celgene) have been evaluated in small phase 2 trials for AL amyloidosis patients and are not generally considered first-line therapy in AL amyloidosis. An exception in the United Kingdom is the oral combination regimen containing thalidomide, cyclophosphamide, and dexamethasone (CTD), which is well tolerated with a high hematologic response rate (74%) and low treatment-related mortality (4%) when used as a first-line therapy and in the relapsed setting for patients initially treated with CyBorD.[60]

The IMiDs are associated with significant fluid retention when combined with dexamethasone. Thirty-five percent of patients receiving CTD had clinically significant fluid retention requiring interruptions in or cessation of therapy. Moreover, lenalidomide and pomalidomide, although active in AL, have been associated with significant side effects.[61-64] The side effects of lenalidomide are particularly complex, because it increases the levels of cardiac biomarkers. The trial testing pomalidomide and dexamethasone in relapsed AL amyloidosis patients found an 18% treatment-related mortality,[62] likely a reflection of the heavily pretreated study population.

Lenalidomide is associated with a 41% hematologic response rate and pomalidomide is associated with a 48% hematologic response rate in patients previously treated with alkylators, bortezomib, and thalidomide. Both lenalidomide and pomalidomide had a low incidence of complete responses (21% and 1%, respectively).[62,63] A higher induction dose (4 mg/day) of pomalidomide combined with dexamethasone induces a higher rate of hematologic response (67%) in patients previously exposed to alkylators, other IMiDs, and proteasome inhibitors. However, the cost of this higher response rate is substantial toxicity (67% grade 3 or 4 adverse events leading to treatment discontinuation in 18%) and significant elevation of NT-proBNP.[64] More recently, preliminary data of a phase 2a trial testing the combination of bendamustine and dexamethasone in relapsed or refractory patients has shown a 45% hematologic response rate, including a 9% complete response rate.[65] For relapsed and refractory disease that is resistant to bortezomib-based regimens, other treatment options include IMiD-based therapy, MDex, or participation in clinical trials.

Supportive Therapy and Solid Organ Transplantation in Systemic AL Amyloidosis

Management of heart failure, peripheral edema, and autonomic dysfunction in AL amyloidosis patients is often challenging (Table 4). Long-term survival has been reported in AL amyloidosis patients with renal involvement treated with renal transplantation (5-year and 10-year graft survival rates, 54% and 26%, respectively).[66] Recurrence of amyloidosis in the transplanted kidney is uncommon in patients who achieve hematologic responses with therapy. We recommend that AL amyloidosis patients with preserved performance status and isolated advanced cardiac, hepatic, or end-stage renal amyloidosis be considered for solid organ replacement if they achieve a hematologic response to therapy or if emergent organ replacement therapy is life-saving (eg, in patients with advanced hepatic involvement) or makes them eligible for SCT. Patients with advanced cardiac amyloidosis (eg, stage III cardiac AL) are not candidates for SCT, and 40% die within a year despite treatment with CyBorD (see Figure 7A online at www.hematologyandoncology.net). If feasible, such patients should be considered for novel antiamyloid therapies or for cardiac transplantation followed by SCT.[67]

Table 4. Supportive Care in AL Amyloidosis

Syndrome	Management Considerations
Autonomic dysfunction	
- Orthostatic intolerance	Midodrine is well tolerated; fludrocortisone can cause fluid retention and edema. Compression stockings may be useful if concomitant lower extremity edema is present. Lifestyle modifications include drinking enough fluids, drinking little to no alcohol, avoiding walks during hot weather, elevating the head of the bed, urinating in a seated position, and standing up slowly.
- Diarrhea, bloating, nausea	Loperamide, diphenoxilate/atropine are useful but have side effects (dryness of mouth, urine retention, dry skin, postural hypotension).
Heart failure	ACE inhibitors and ARBs are poorly tolerated. Small dosages of BBs can be tolerated, but value of afterload reduction is unknown. CCBs can exacerbate edema, postural hypotension, and tachycardia. Digoxin can bind amyloid and should be avoided.
Cardiac dysrhythmias	No known effective therapy (though often the cause of death in patients with cardiac involvement). Amiodarone is commonly used. AICDs and LVADs remain experimental, but likely are useful in selected patients with preserved EF. Cardiac death often occurs owing to EMD rather than arrhythmia.
Edema	Diuretics are mainstay of treatment, but standard dose is often poorly tolerated. Exacerbation of orthostatic hypotension, azotemia, and hypokalemia can be common, needing frequent monitoring of renal function, volume status, and electrolytes. Rapid diuresis (eg, with intravenous standard dose) invariably leads to hypotension and renal failure. Albumin infusion is costly but some patients benefit from short-term use until euvolemia is restored.

ACE, angiotensin-converting enzyme; AICD, automatic implantable cardioverter defibrillator; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; EF, ejection fraction; EMD, electromechanical dissociation; LVAD, left ventricular assist device.

Conclusion

Management of patients with AL amyloidosis remains a challenge for physicians and an ordeal for patients and their families. Earlier diagnosis using the FLC assay and cardiac biomarkers in high-risk populations (eg, MGUS or SMM patients) will reduce the fraction of patients who die of advanced heart disease within months of diagnosis. Moreover, tracking patients with known MGUS or SMM would become more systematic if newer imaging techniques were available to diagnose AL amyloidosis earlier. Making immunoglobulin light-chain variable region germline gene studies routinely available would also be beneficial, because the majority of AL amyloidosis cases are caused by only a few germline donors.[68] Our current overall algorithm for therapy of AL amyloidosis patients is depicted in Figure 8 (see online at www.hematologyandoncology.net).

For AL amyloidosis patients who respond to initial therapy and survive for years, the issues of survivorship are striking. Medical, financial, and psychologic burdens in AL amyloidosis are different than in other diseases because of the often-persistent organ damage. Persistent proteinuria can lead to end-stage renal disease, and cardiac scarring to arrhythmias, even 5 years or more after achieving a complete hematologic response. The risk of relapse and the need for further therapy is also a source of anxiety with each follow-up visit. For the most at-risk population—those with advanced cardiac involvement at diagnosis—the use of newer-generation left ventricular assist devices should be studied in clinical trials, given the current limitations on cardiac transplant.

New therapies are needed to reduce the recurrence rate for patients who respond to initial therapy, and maintenance strategies may be useful in this regard. Furthermore, the monoclonal antibodies currently being tested in myeloma should also be tested in patients with AL, particularly the human anti-CD38 monoclonal antibody daratumumab, which has single-agent activity in myeloma.[69] Moreover, a novel therapy currently in preclinical development uses RNA interference specific for light-chain constant-region consensus sequences in order to directly target light chain produced by plasma cells .[70,71]

In summary, although the pace of progress is rapid from a scientific and drug-development point of view—as in many incurable and fatal diseases—it still remains much too slow for newly diagnosed patients and their families, for whom "time is life" and life is what hangs in the balance.

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Disclosures

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Supporting Online Material

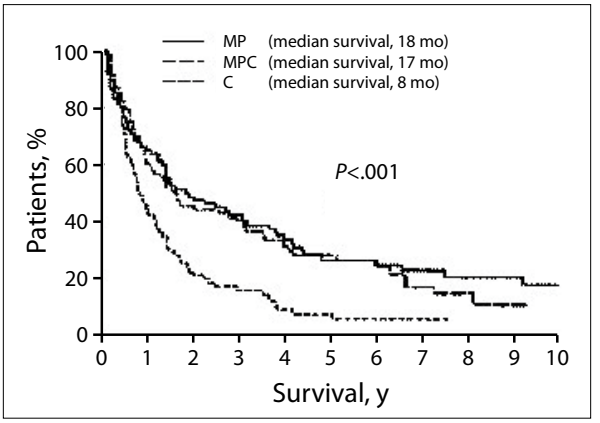

Figure 1. Historical outcomes of therapy for systemic AL amyloidosis: Kaplan-Meier plot of a large single-center phase 3 trial conducted from 1982 to 1995. Patients were randomly assigned to receive melphalan and prednisone; melphalan, prednisone, and colchicine; or colchicine alone. Median survival in the groups receiving melphalan and prednisone was 18 months.

C, colchicine; mo, months, MP, melphalan and prednisone; MPC, melphalan, prednisone, and colchicine; y, years.

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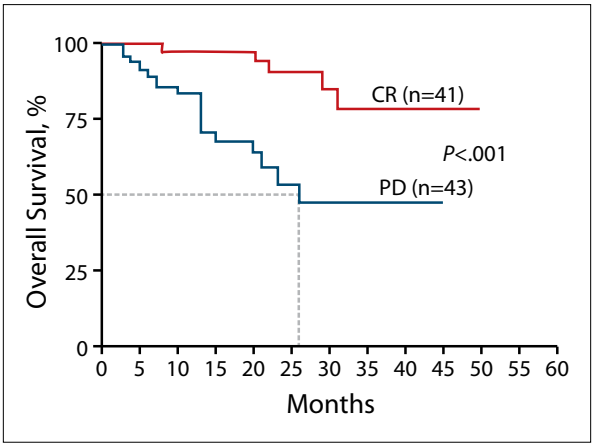

Figure 2. Historical outcomes of therapy for systemic AL amyloidosis: early single-center experience with melphalan plus stem cell transplant.

CR, complete response; PD, progressive disease.

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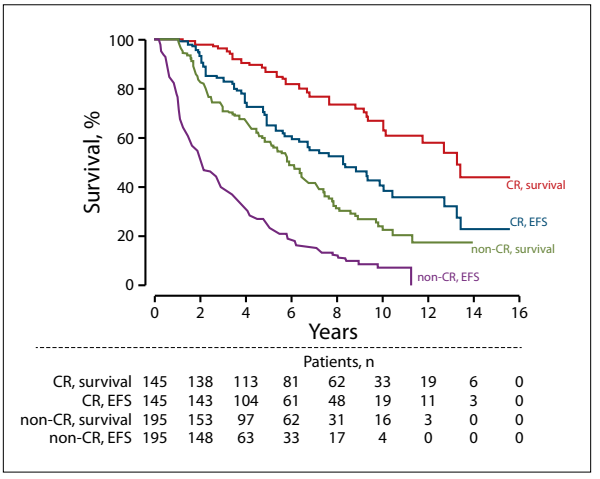

Figure 3. Historical outcomes of therapy for systemic AL amyloidosis: melphalan plus stem cell transplant experience from 1994 to 2010 in 421 patients at a single center is depicted, showing the impact on survival of achieving a complete hematologic response.

CR, complete response; EFS, event-free survival.

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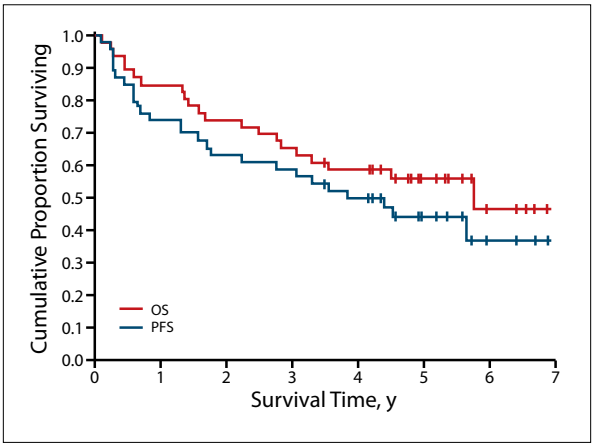

Figure 4. Historical outcomes of therapy for systemic AL amyloidosis: overall and progression-free survival of patients treated with oral melphalan plus dexamethasone in a phase 2 trial.

OS, overall survival; PFS, progression-free survival; y, years.

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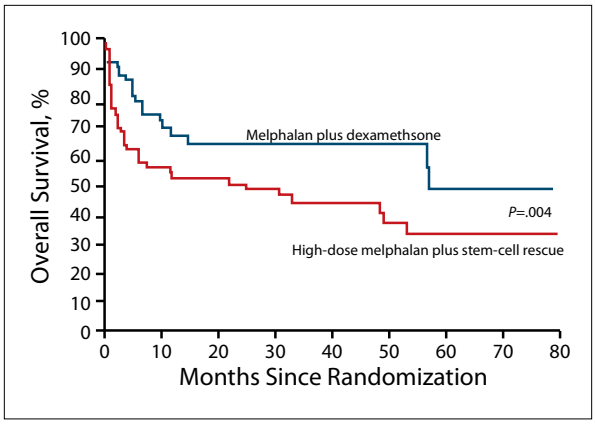

Figure 5. Historical outcomes of therapy for systemic AL amyloidosis: results of the French multicenter phase 3 trial found that oral melphalan plus dexamethasone improved overall survival compared with melphalan plus stem cell transplant.

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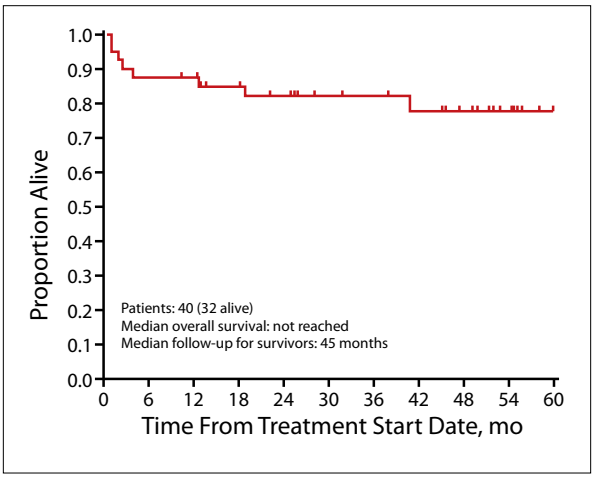

Figure 6. Current outcomes in the bortezomib era: overall survival of patients treated with risk-adapted melphalan plus stem cell transplant and bortezomib-based consolidation post-stem cell transplant, achieving a complete response rate of 60% and prolonged survival.

mo, months.

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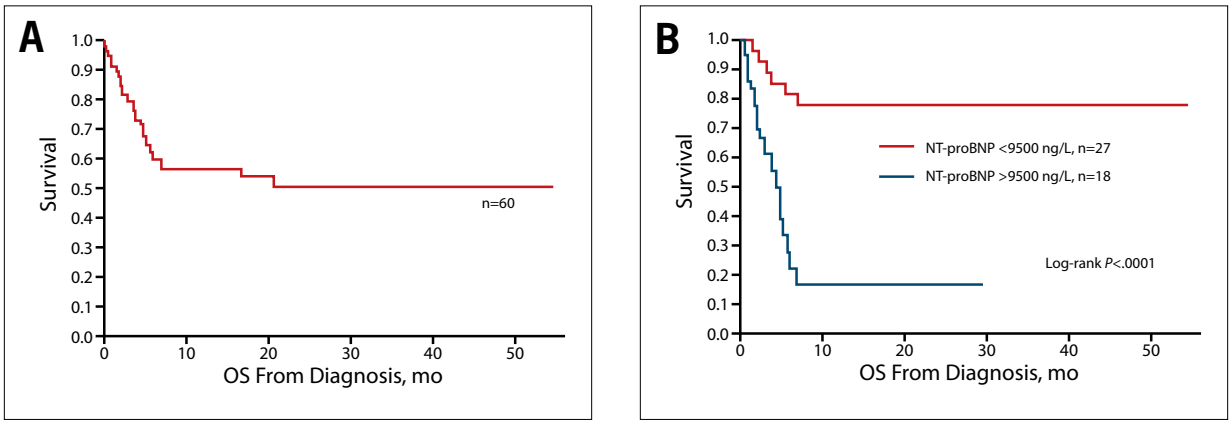

Figure 7. Current outcomes in the bortezomib era. **A,** Overall survival of patients with cardiac stage III disease, ineligible for stem cell transplant, who were treated with CyBorD; of note, although 40% of patients died within the first year, the 60% survival at 2 years represents progress for these patients whose prognosis is poor. **B,** Patients with elevated NT-proBNP at diagnosis have dramatically decreased overall survival rates, despite CyBorD treatment.

CyBorD, cyclophosphamide, bortezomib, and dexamethasone; NT-proBNP, N-terminal brain-type natriuretic peptide; mo, months; OS, overall survival.

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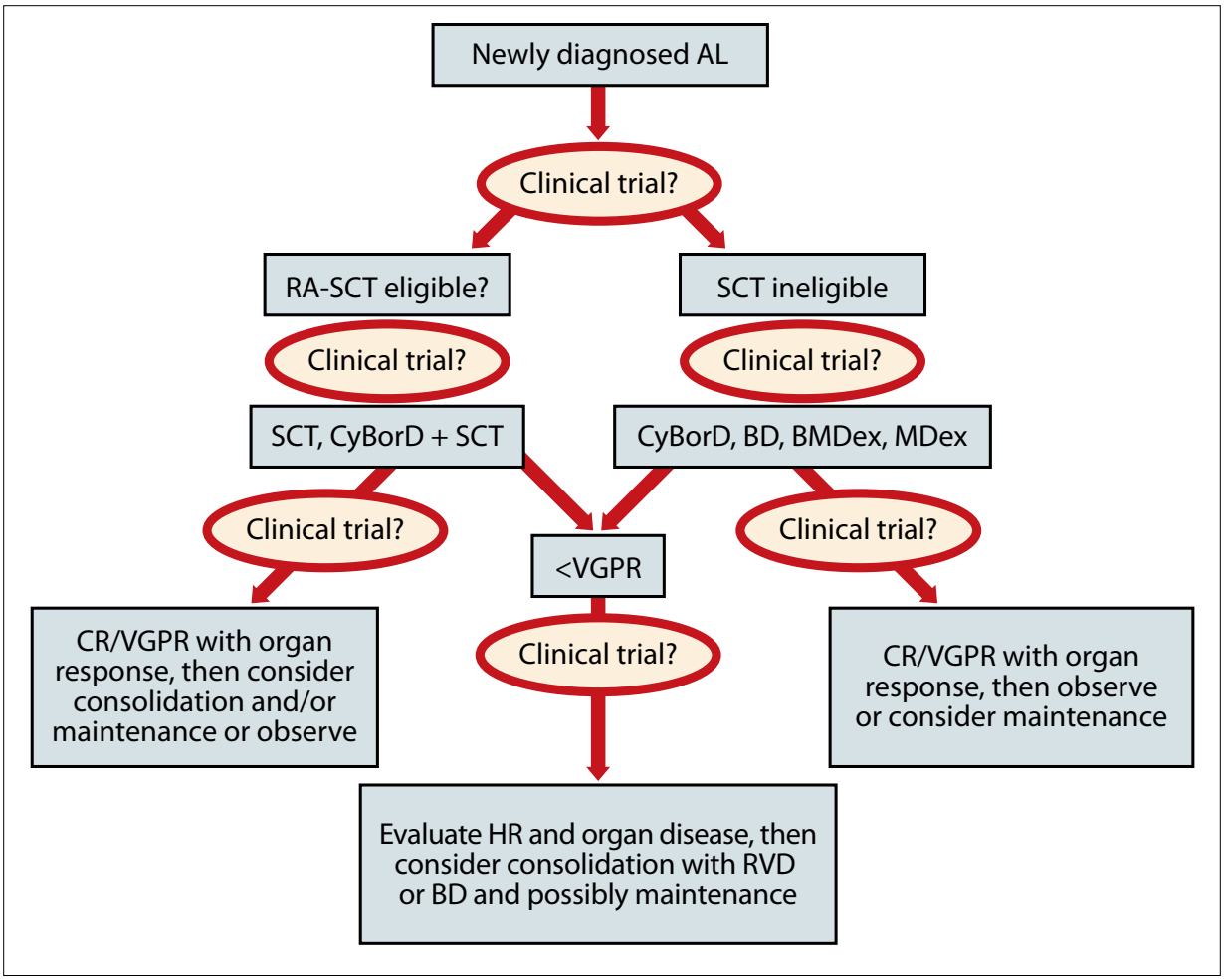

Figure 8. The current algorithm used for newly diagnosed patients, dividing them into stem cell transplant (SCT)-eligible and SCT-ineligible for initial therapy, and then into those achieving a very good partial response or better. Enrolling patients in clinical trials should be considered at every stage of treatment.

AL, light-chain amyloidosis; BD, bortezomib plus dexamethasone; BMDex, bortezomib, melphalan, and dexamethasone; CR, complete response; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; HR, hematologic response; MDex, melphalan plus dexamethasone; NT-proBNP, N-terminal brain-type natriuretic peptide; RA-SCT, risk-adapted stem cell transplant; RVD, lenalidomide, bortezomib, and dexamethasone; SCT, stem cell transplant; VGPR, very good partial response.