Review

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Recent Advances in the Diagnosis, Risk Stratification, and Management of Systemic Light-Chain Amyloidosis

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Abstract
The term amyloidosis refers to a group of disorders in which protein fibrils accumulate in certain organs, disrupt their tissue architecture, and impair the function of the effected organ. The clinical manifestations and prognosis vary widely depending on the specific type of the affected protein. Immunoglobulin light-chain (AL) amyloidosis is the most common form of systemic amyloidosis, characterized by deposition of a misfolded monoclonal light-chain that is secreted from a plasma cell clone. Demonstrating amyloid deposits in a tissue biopsy stained with Congo red is mandatory for the diagnosis. Novel agents (proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, venetoclax) and autologous stem cell transplantation, used for eliminating the underlying plasma cell clone, have improved the outcome for low- and intermediate-risk patients, but the prognosis for high-risk patients is still grave. Randomized studies evaluating antibodies that target the amyloid deposits (PRONTO, VITAL) were recently stopped due to futility and currently there is an intensive search for novel treatment approaches to AL amyloidosis. Early diagnosis is of paramount importance for effective treatment and prognosis, due to the progressive nature of this disease.

Introduction

Light-chain (AL) amyloidosis is the most common form of systemic amyloidosis, accounting for 70% of patients with amyloidosis [1–3]. It is characterized by deposition of a misfolded monoclonal light-chain that is secreted from a malignant plasma cell clone, because the defective protein does not conform to the alfa-helical configuration of most proteins but rather forms beta pleated sheets [4]. This structure is insoluble and deposits in tissues and interferes with an organ's normal function [5].

AL amyloidosis (historically referred to as primary amyloidosis) is an uncommon disorder and its exact incidence is unknown. In the USA the incidence is 9–14 cases per million person years [6]. AL amyloidosis is a disease of the elderly and the incidence increases with age

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[6]. The median age at diagnosis is 63 years [7], and 1.3% of patients are under the age of 34 years. There is a male predominance, with men accounting for 55% of patients [7]. AL amyloidosis occurs in all races and geographic locations, but data are limited regarding the incidence of AL amyloidosis across different ethnic groups.

Improved prognostication and response assessment allows us to safely apply treatments originally developed for multiple myeloma (MM). To continue improving patient prospects, early and accurate diagnosis and meticulous treatment choices are essential. Making the diagnosis remains a great challenge even for hematologists who are experts in MM. Whenever possible, patients should be treated in the context of clinical trials and preferably treatment undertaken in selected centers experienced in treating complex patients [8]. In this review, we summarize the data on the pathogenesis, diagnosis, risk stratification, and management of AL amyloidosis patients.

Patient 1

A 71-year-old man presented to his primary care physician in 2017 with a 1-year history of orthostatic hypotension, diarrhea, and loss of 18 kg. He had also developed urinary emptying problems and underwent self-catheterization starting in August 2017. He was diagnosed as CIPD (chronic inflammatory demyelinating polyneuropathy) and began treatment with IVIG (intravenous immunoglobulin) and plasma exchange. In February 2018 he underwent a biopsy from a mass in his left kidney and afterwards bled and required embolization and 13 units of packed cells. He was evaluated at the Mayo Clinic by a gastroenterologist in May 2018. A colonoscopy was performed for persistent diarrhea and was biopsy positive for amyloidosis. Mass SPECT showed this to be AL amyloidosis. The amyloidosis manifested itself as autonomic failure with orthostatic hypotension, diarrhea, and an autonomic bladder.

Patient 2

A 63-year-old man was diagnosed with lambda (λ)-MGUS (monoclonal gammopathy of undetermined significance) in 2015, during evaluation of L5/S1 radiculopathy. He was monitored and reassured that his proteins had not changed over time. The λ-free light-chain (FLC) was 9.2 mg/dL, and the kappa (κ) was 0.9 mg/dL. In September 2016 he was admitted due to dyspnea on exertion and fatigue. In December 2017, during his annual physical evaluation, his ECG was abnormal, and he was seen by a cardiologist. Echocardiogram showed an increased wall thickness and an MRI of the heart was performed which showed evidence of infiltrative cardiomyopathy, suggestive of amyloidosis. A fat aspiration performed twice was negative for amyloidosis. His showed a nephrotic range proteinuria of 1,092 mg in a 24-h collection. He underwent a CT-guided kidney biopsy which showed light-chain amyloid deposits, predominantly vascular. The managing hematologist was falsely reassured by the stable M protein that no serious plasma cell dyscrasia was developing. This is an example of a delay in the diagnosis of AL amyloid that may have detrimental consequences on a patient's prognosis [9]. It is important to emphasize that abdominal fat aspirate is an operator-dependent test with a sensitivity of 60–68% and a negative result should be interpreted with caution.

Diagnosis and Typing

The clinical manifestations of AL amyloidosis depend on the number and the extent of organ involvement but are usually not specific. The most common symptoms associated with amyloidosis are weight loss, fatigue, edema, and dyspnea on exertion [10–12]. Weight loss can occur regardless of diarrhea or vomiting, and the mechanism of weight loss is unclear but might be a result of progressive heart failure. Lightheadedness and orthostatic syncope are rather frequent and can result from reduced intravascular volume due to hypoalbuminemia, the use of diuretics, and autonomic failure [13]. The most frequently affected organs are the heart (71%), kidneys (58%), gastrointestinal (GI) tract (22%), nervous system (23%), and liver (16%). Soft tissue deposits should raise clinical suspicion to the diagnosis but are rather uncommon (10%) [14]. In some patients only one organ is affected, whereas in others several organs would be involved.

Renal Involvement

Renal involvement occurs in 58% of AL amyloidosis patients and usually presents as a nonselective proteinuria or nephrotic syndrome. The patient may present with peripheral edema, anasarca, foaming urine, or symptoms of uremia. Laboratory tests may show elevated lipid levels, hypoalbuminemia, and nonselective proteinuria. Ultrasound or CT may demonstrate enlarged kidneys.

Cardiac Involvement

Heart involvement is the most important prognostic factor in AL amyloidosis patients and occurs in 71% of AL amyloid patients. The patients present with fatigue, dyspnea at exertion, peripheral edema, jugular venous dis-

tention, and pleural effusion. Other manifestations can include arrhythmia causing sudden death or syncope, and rarely myocardial infarction due to the accumulation of amyloid in the coronary arterioles. Myocardial damage caused by the amyloidogenic light-chains can result in elevation of N-terminal pro-brain natriuretic peptide (NT-proBNP) [15]. ECG can demonstrate a low voltage in limb leads (defined as all limb leads <0.5 mV; in 46–70%) [12], a pseudoinfarct pattern with poor R-wave progression in chest leads (47%), and atrial fibrillation [16].

Echo may demonstrate thickening of left ventricular walls and interventricular septum, reduced strain, and preserved ejection fraction. These findings reflect the fact that cardiac amyloidosis is predominantly a disease of the diastole. In severe involvement, atrial thrombi may be present even in a sinus rhythm due to atrial electromechanical dissociation that causes atrial standstill [12]. It should be noted that rapid clinical deterioration can result from atrial fibrillation and the thromboembolic risk is elevated. The gold standard for diagnosing cardiac amyloidosis is endomyocardial biopsy, but noninvasive cardiac imaging can replace the need for cardiac biopsy. Cardiac MRI late gadolinium enhancement was shown to be highly sensitive (80–100%) with a negative predictive value of 85–100%, while the specificity and positive predictive values are 80–94 and 81–92%, respectively [17, 18]. Cardiac MRI is unable to reliably differentiate between the various subtypes of cardiac amyloidosis. Scintigraphy with Tc-99m-pyrophosphate (^{99m}Tc-PYP) is a noninvasive and widely available method useful in identifying patients with the ATTR subtype [19]; however, this test still needs to be standardized [20].

GI Involvement

GI involvement my manifest itself as constipation, diarrhea, early satiety, GI bleeding, heartburn [21], nausea and vomiting due to gastroparesis [22], and weight loss. Laboratory testing may show hypoalbuminemia and anemia, and imaging tests may demonstrate a dilated esophagus and signs of decreased peristalsis, as well as thickening of the stomach wall or small intestine.

Involvement of the Soft Tissues

AL amyloidosis patients may present with macroglossia, hoarseness, dysarthria, obstructive sleep apnea, periorbital purpura often occurring after mild trauma or physical activity, submandibular gland swelling, xerostomia, and periarticular involvement causing the shoulder pad sign (enlargement of the anterior shoulder due to fluid in the glenohumeral joint or amyloid infiltration of the synovial membrane and surrounding structures; Fig. 1). Macroglossia (Fig. 2) can cause significant morbidity due to problems with breathing, talking, and chewing, resulting in the need for feeding tubes and tracheostomy.

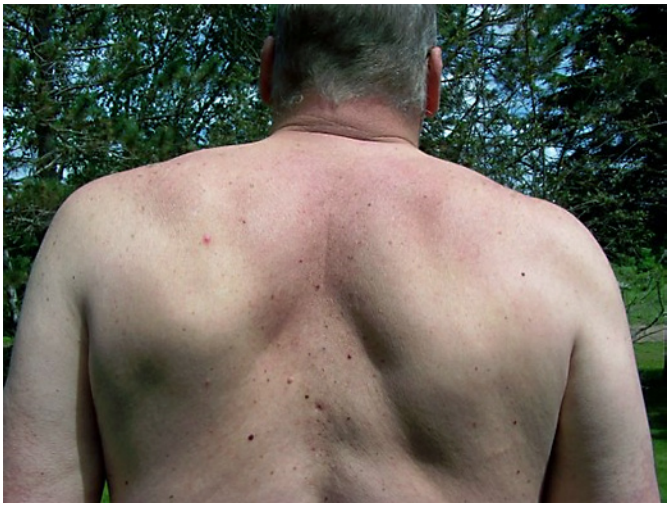

Fig. 1. Shoulder pad sign.

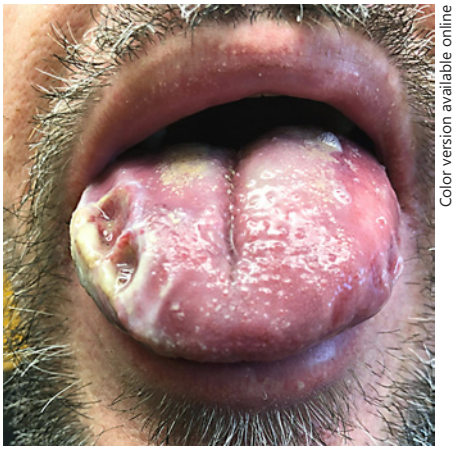

Fig. 2. Macroglossia.

Jaw claudication (pain while chewing) reflects vascular amyloid deposition and may cause a great deal of morbidity. Carpal tunnel syndrome sometime precedes the tissue diagnosis of AL amyloidosis by years (range 1 month to 9.3 years) [12].

Nerve Involvement

Mixed sensory and motor peripheral neuropathy (20%) and autonomic neuropathy (15%) are prominent features in AL amyloidosis. Symptoms of numbness, paresthesia, and pain are frequently noted resulting from the

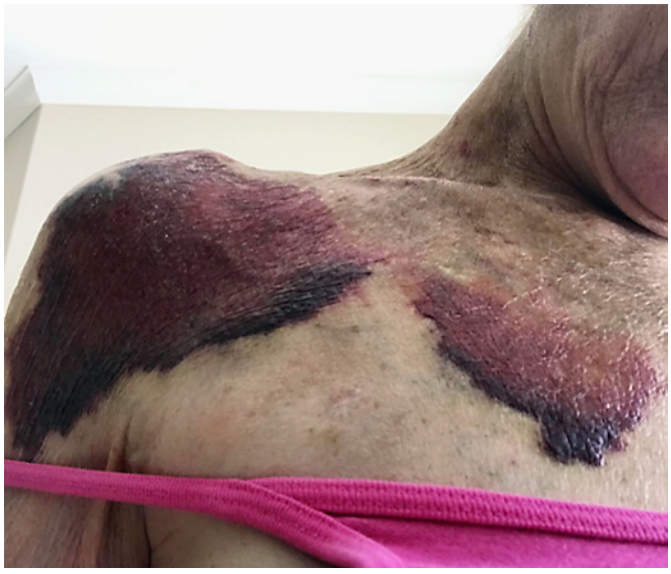

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Fig. 3. Upper extremity purpura.

involvement of peripheral nerves, especially the median nerve within the carpal tunnel. Symptoms of bowel or bladder dysfunction and orthostatic hypotension are caused by autonomic nervous system damage. Patients with neurologic symptoms should be evaluated with electromyography, bearing in mind that this test can be normal because the neuropathy is most typically due to damage to the small unmyelinated nerve fibers.

Coagulation Abnormalities

AL amyloidosis may be associated with a bleeding diathesis (Fig. 3). In a retrospective report of 337 patients, abnormal bleeding and abnormal coagulation tests were seen in 28 and 51%, respectively [23]. Subnormal factor X activity was found in 22 cases out of 154 who were studied further (14%) [23]. The proposed mechanisms include factor X deficiency due to binding to amyloid fibrils, decreased synthesis of coagulation factors due to advanced liver disease, and acquired von Willebrand disease. However, some patients with abnormal bleeding have no abnormality in any coagulation test. In such cases amyloid infiltration of blood vessels should be suspected [24].

The diagnosis of AL amyloidosis requires the demonstration of amyloid fibrils in a tissue sample taken from the suspected affected organ (heart, kidney, liver, etc.) or from a surrogate site (abdominal fat pad, bone marrow). Biopsy of the iliac crest bone marrow [25] combined with abdominal subcutaneous fat aspiration [26] will identify amyloid deposits in 85% of patients with AL amyloidosis. The abdominal fat aspirate is a simple and minimally invasive test, although its interpretation requires expertise [27]. The sensitivity of abdominal fat pad aspiration is 74% for κ-AL and 84% for λ-AL amyloidosis [28]. The sensitivity of salivary gland biopsy is around 90% and it may be used if experience with fat aspiration is lacking [29]. If AL amyloidosis is still suspected in the setting of negative surrogate site biopsies, the affected organ should be biopsied. The sensitivities of biopsies to the detection of amyloid are listed in Table 1.

Table 1. The sensitivity of various biopsy sites in detecting amyloid fibrils

Organ	Sensitivity reported, %
Abdominal fat pad	60–80
Rectal biopsy	50–70
Bone marrow biopsy	50–55
Skin biopsy	50
Kidney	90
Liver	90

The proposed checklist for a newly diagnosed amyloid patient is listed in Table 2. The diagnostic algorithm for a patient with suspected amyloidosis is presented in Figure 4.

The presence of a monoclonal gammopathy does not necessarily mean that the diagnosis is AL amyloidosis. It should be noted that MGUS is very prevalent in patients over the age of 65 years, highlighting the need for amyloid typing to avoid misdiagnosis [28].

Immunohistochemistry is the most widely available method for amyloid typing, but the specificity and sensitivity are low. This typing method is problematic due to high background staining caused by serum contamination and epitope loss caused by protein cross-linking after formalin fixation [30]. When performed by a highly specialized pathologist combined with clinical data and genotyping, it may lead to accurate amyloidosis classification [31].

Immunoelectron microscopy (IEM) with gold-labelled antibodies is highly sensitive, but is not available in most centers. IEM of abdominal fat aspirates is an effective tool in the routine diagnosis of systemic amyloidosis. One study compared the performance of IEM of abdominal fat aspirates with Congo red-based light microscopy and showed that they were equally sensitive (75–80%) but the IEM was significantly more specific (100 vs. 80%) [28].

Table 2. Suggested diagnostic evaluation for a newly diagnosed amyloid patient

Blood tests	Urinary tests	Imaging and invasive tests	Others
Complete blood count	Electrophoresis of the serum and urine	Unilateral bone marrow aspirate and biopsy with immunohistochemical staining for κ and λ and Congo red staining for amyloid and FISH[1]	Blood pressure to asses for orthostatic hypotension
Liver and renal function	24-h urinary protein	Bone imaging[2]	Fertility preservation
Protein electrophoresis		Electrocardiogram	
Immunofixation of the serum		Echocardiogram	
FLC assay		Cardiac MRI optional	
Troponin T and NT-proBNP		Electromyography and nerve conduction studies if symptomatic	
Thyroid-stimulating hormone		Gastric emptying test if pseudo-obstruction	
Prothrombin time and partial thromboplastin time			

[1] Suggested FISH panel: t(11;14), t(4;14), t(14;16), t(14;20), trisomies, 1q+, and del(17p).
[2] Should be performed in patients with ≥10% bone marrow plasma cells.

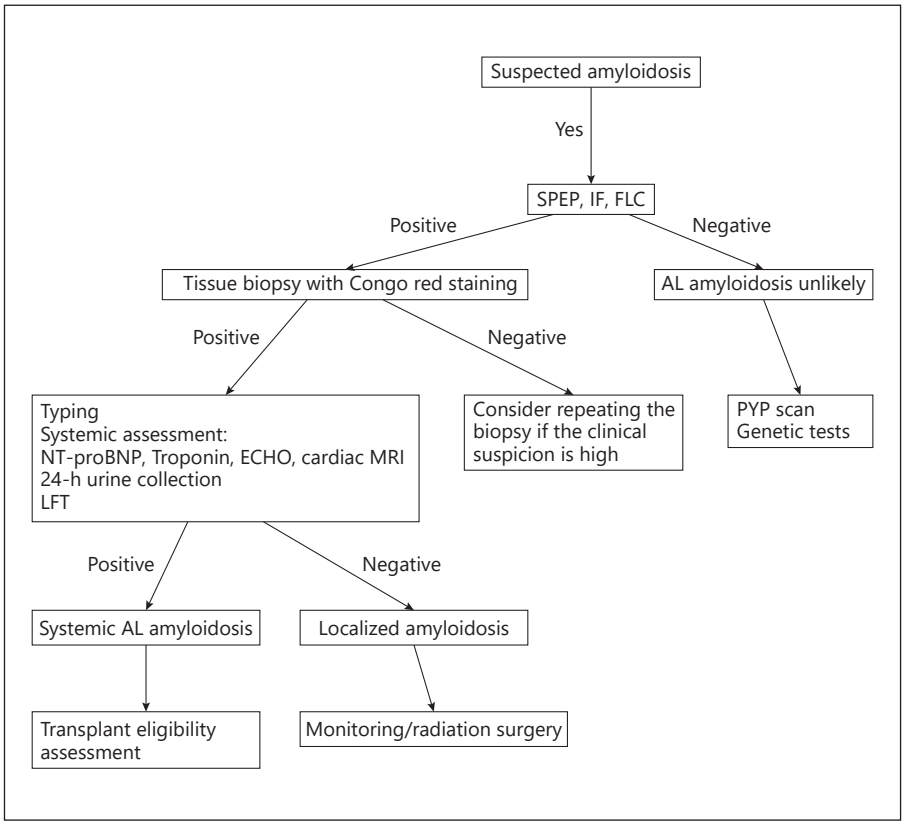

Fig. 4. Diagnostic algorithm for the evaluation of a patient with suspected amyloidosis. SPEP, serum protein electrophoresis; IF, immunofixation; FLC, free light-chains; PYP, pyrophosphate; NT-proBNP, N-terminal pro-brain natriuretic peptide; ECHO, echocardiology; MRI, magnetic resonance imaging; LFT, liver function tests.

Laser microdissection and mass spectrometry-based proteomic analysis is considered the gold standard for the typing of amyloid with specificity of 100% and sensitivity of 90% [30], but it is available in few centers. This analysis is done in paraffin-embedded biopsies [30].

Genetic tests for the exclusion of hereditary amyloidosis should be considered, especially in patients with no evidence of plasma cell disorder and in patients with a family history of the amyloidosis. Serum amyloid P component (SAP) scintigraphy is not widely available but can visualize and quantify amyloid infiltration in the kidneys, liver, spleen, adrenals, and bone (less helpful in detecting cardiac involvement). SAP scintigraphy cannot differentiate the various types of amyloidosis, but it can be used to follow the response to therapy. The scan may be positive even when tissue biopsy has been negative [32].

The diagnostic criteria according to the International Myeloma Working Group (IMWG) requires the presence of all the following four criteria [33]:

1 Presence of an amyloid-related systemic syndrome (e.g., renal, liver, heart, GI tract, or peripheral nerve involvement).
2 Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy).
3 Evidence that amyloid is light-chain-related, established by direct examination of the amyloid using mass spectrometry-based proteomic analysis or IEM.
4 Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal FLC ratio, or clonal plasma cells in the bone marrow).

Localized versus Systemic Amyloidosis

Deposition of amyloid may occur in individual organs, in the absence of systemic involvement, and determining whether the amyloidosis is localized or systemic might be challenging. However, differentiating localized from systemic amyloidosis is crucial regarding treatment decisions and prognosis. Amyloid lesions are distinct from plasmacytomas, in which cellular elements dominate with associated background amyloid material [34].

The etiology of localized deposition is unknown, but it is hypothesized that deposits result from local synthesis of amyloid protein, rather than the deposition of light-chains produced in the bone marrow [34]. Amyloid fibrils in localized disease are usually light-chain derived. The mean age at the time of diagnosis is similar to that in systemic amyloidosis [34] and is considered rare, although the incidence is unknown.

Localized amyloidosis occurs in a variety of organ systems, including the skin and nails [35], larynx [36], lung [37] bowel [38], orbit [39], or urinary tract [40], including the renal pelvis, ureter, bladder, and urethra. Evolution of localized amyloidosis to systemic amyloidosis is rare [37]. The course of the disease is relatively benign in most patients with no effect on life expectancy [41], but severe damage to the affected organ can ultimately occur. If symptomatic, localized amyloidosis can be treated by radiotherapy or by local excision using either classic surgical techniques or laser-based excision [8, 39]. Coexisting autoimmune diseases were reported in 7% of patients [39].

Chromosomal Abnormalities in Amyloidosis

Fluorescence in situ hybridization (FISH) is prognostic in untreated AL amyloidosis and may guide therapeutic decisions. Often the amyloidogenic clone is characterized by chromosomal abnormalities [42]. The most frequent genetic abnormalities in AL amyloidosis are t(11;14) (50%) [42], monosomy 13/del(13q) (36%), and trisomies (26%) [43].

The presence of t(11;14) is associated with poorer outcomes with bortezomib-based and immunomodulatory (IMiD)-based therapy. These patients have a lower rate of very good partial response (VGPR) or better, and an inferior overall survival (OS) when treated with bortezomib [44]. Trisomies were associated with a shorter OS, reaching statistical significance only for patients treated with melphalan [43]. Patients with t(11;14) should be considered for autologous stem cell transplantation (ASCT) or standard-dose melphalan at diagnosis because the survival disadvantage may be abrogated. In a study assessing the prognosis of AL amyloidosis patients treated with high-dose melphalan (HDM) chemotherapy and ASCT, HDM was found to be safe, with only 1 out of 123 patients dying because of the treatment, and with a complete remission (CR) rate of 34%. Patients harboring t(11;14) had an improved CR rate, translating into a prolonged event-free survival [45].

t(4;14) and t(14;16) were rarely found in AL, accounting only for 3 and 4% of patients, respectively [42]. The frequency of del(17p) in AL amyloidosis is 3% [43]. These MM high-risk FISH aberrations, t(4;14), t(14;16), and del(17p), conferred no adverse prognosis in patients treated with bortezomib [44]. This raises the possibility that bortezomib may abrogate the poor prognosis of high-risk aberrations [44]. However, these high-risk cy-

togenetic aberrations may confer an unfavorable prognosis in HDM-treated patients [45].

Gain of 1q21 is less frequent in AL amyloidosis than in MM, being found in less than 20% of patients [42]. Gaining 1q21 conferred no adverse prognosis in patients treated with bortezomib [44].

In a trial assessing 44 newly diagnosed patients with AL amyloidosis and del(17p), 95% had cardiac involvement, including 44% with Mayo stage III; 66% received bortezomib-based therapy. Approximately half achieved deep responses with a median time to best response of 4 months. The median OS and progression-free survival (PFS) were 49 and 32 months, respectively. The cardiac stage, hematologic response, and del(17p) percentage all have an impact on outcomes [46].

Risk Stratification

Cardiac involvement is the major prognostic factor for survival, and changes in cardiac function after therapy can be easily assessed by monitoring NT-proBNP. Changes in both FLC and NT-proBNP predicted survival 3 months after treatment initiation. This has been validated in 98 patients undergoing ASCT [47].

The prognostic significance of a high-sensitivity (hs) cTnT assay, NT-proBNP, and cardiac troponin I was evaluated in 171 patients with AL amyloidosis at presentation and 6 months after treatment. The response and progression of NT-proBNP were defined as more than 30% and more than 300-ng/L changes. The median survival was 10.6 months if hs-cTnT was above 77 ng/L. After treatment, response and progression of NT-proBNP by more than 75% were an independent prognostic factor [48].

Among 271 patients undergoing stem cell transplantation, troponin T was a predictor of treatment-related mortality. Patients with troponin T levels of 0.06 μg/L or higher had a day-100 all-cause mortality rate of 28%. Patients with troponin T levels less than 0.06 μg/L had a day-100 all-cause mortality rate of 7% [49]. These criteria are used to exclude patients from ASCT [50].

The stage of amyloidosis is an important predictor of outcome. According to the revised Mayo Clinic staging system, patients were assigned a score of 1 for each of dFLC ≥18 mg/dL, cTnT ≥0.025 ng/mL, and NT-proBNP ≥1,800 pg/mL, creating stages I–IV with scores of 0–3 points. The median OS was 94.1, 40.3, 14, and 5.8 months, respectively [2]. Patients with AL amyloidosis and bone marrow infiltration of more than 10% plasma cells have a poor prognosis, similar to that of patients with overt MM [51].

A study that evaluated the relationship between FLC levels and clinical characteristics in 730 patients with newly diagnosed AL amyloidosis showed that the type of light-chain impacts the spectrum of organ involvement (patients with κ-AL had more GI and liver involvement, while renal involvement was more prevalent among patients with λ-AL). The OS was similar for κ-AL and λ-AL, and OS was also shorter among those with a higher dFLC [52].

Immunoparesis has a negative impact on response and survival in newly diagnosed AL amyloidosis. In the subset of patients with cardiac involvement, severe immunoparesis conferred very poor outcomes [53]. A total of 998 newly diagnosed AL amyloidosis patients were evaluated for immunoparesis. Patients with suppression of all the uninvolved immunoglobulins were less likely to achieve VGPR or better. Patients with suppression of all the uninvolved immunoglobulins had a shorter OS [54].

In a case-control study of 39 patients treated for AL amyloidosis with biopsy-proven kidney involvement, the composite scarring injury score (CSIS) and amyloid score (AS) were applied to each kidney biopsy. Patients with an AS ≥7.5 had a significantly higher incidence of end-stage kidney disease than those with an AS <7.5 [55].

A study conducted at the Mayo Clinic evaluated the organ response of newly diagnosed AL amyloidosis patients to grade the depth of response. The median time to cardiac, renal, and hepatic response was 9.4, 6, and 6.1 months, respectively. In all organs, the depth of organ response correlated with OS. The authors defined four organ response criteria groups: complete organ response (nadir NT-proBNP ≤400 pg/mL; nadir proteinuria ≤200 mg per 24 h; nadir alkaline phosphatase ≤2× the lower limit of normal); very good partial organ response (>60% reduction in the parameter not meeting the complete organ response definition); partial organ response (31–60% reduction in the parameter), and nonresponders (≤30% reduction in the organ response parameter) [56].

Treatment

General Principles

Management of AL amyloidosis should be multidisciplinary, involving experts in hematology, cardiology, nephrology, gastroenterology, and neurology. Few prospective randomized phase III trials have been conducted in

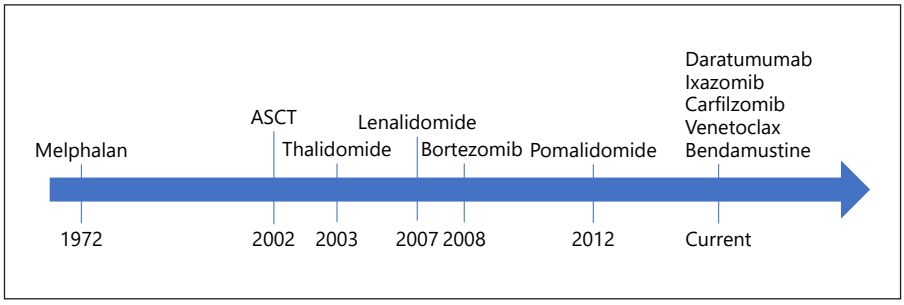

Fig. 5. The timeline of treatments for AL amyloidosis.

the field of AL amyloidosis and most published recommendations are based on phase II studies, retrospective studies, and case series. Whenever possible, patients should be treated in the context of clinical trials and treatment undertaken in selected centers experienced in treating complex patients [8].

The first step in deciding how to treat a newly diagnosed AL amyloid patient is determining whether they are eligible for ASCT. Appropriate patient selection is essential to avoid treatment-related mortality. The decision should be made on an individual basis while weighting the risk-benefit ratio and the patient's wishes.

The eligibility criteria for ASCT in AL amyloidosis are: age ≤70 years, troponin T <0.06 ng/mL, systolic blood pressure ≥90 mm Hg, creatinine clearance ≥30 mL/min (unless on chronic stable dialysis), Eastern Cooperative Oncology Group (ECOG) performance status ≤2, New York Heart Association (NYHA) functional status class I or II, no large pleural effusions, no dependency on oxygen therapy, and no more than two organs significantly involved (liver, heart, kidney, or autonomic nerve) [50]. Figure 5 shows the timeline of treatments for AL amyloidosis.

Supportive Care Treatment

Diuretics are the mainstay of therapy for cardiac and renal amyloidosis patients, helping to reduce edema, but may cause hypotension and creatinine elevation. A close follow-up of weight, blood pressure, creatinine, and potassium levels is required. Patients that develop significant hypotension may benefit from midodrine.

Atrial fibrillation is not uncommon in cardiac amyloid patients and treatment with digoxin was considered contraindicated due to the assumption that amyloid fibrils bind digoxin making patients with amyloid cardiomyopathy sensitive to this drug [57]. However, based on a recently published retrospective trial, we recommend using digoxin at lower doses while frequently monitoring drug concentration and closely monitoring electrolytes and kidney function. The efficacy of implantable cardioverter-defibrillators (ICDs) has not been demonstrated prospectively. In a report from the Mayo Clinic of 33 patients with AL amyloidosis who received an ICD, there was a high rate of appropriate ICD shocks, but this did not translate into an OS benefit [58].

Bradyarrhythmias proceeded terminal cardiac decompensation in many patients with severe cardiac AL amyloidosis with implantable loop recorders. However, pacemaker insertion failed to salvage patients with bradyarrhythmias in a study of newly diagnosed patients with severe symptomatic cardiac AL amyloidosis [59].

Selected patients, with single organ involvement and in prolonged deep hematological response, may undergo cardiac, renal, or liver transplantation [60, 61]. However, most patients with advanced cardiac AL amyloidosis are not candidates for these procedures and recurrence of amyloidosis in the allograft is not uncommon. Heart transplantation followed by SCT was reported in 5 patients, 2 of whom died of relapsed amyloidosis [62]. In 11 patients that underwent a heart transplantation followed by ASCT, 2 died of complications from the SCT (18% transplant-related mortality). The 1- and 5-year survival rates were 82 and 65%, respectively [63]. Renal transplantation can be considered, especially in young patients with a good performance status [64].

Nutritional evaluation is an integral part of the clinical assessment of AL amyloidosis. Malnutrition at diagnosis has been shown to predict mortality in patients with AL amyloidosis independently of cardiac stage and response to treatment [65]. It is still unknown whether nutritional support influences patient outcome.

AL amyloidosis patients are at risk of infections due to the loss of immunoglobulins and the use of immunosuppressive therapy. However, prophylactic antibiotics is not routinely recommended.

Chemotherapy Treatment

The major goal of therapy is to destroy the amylogenic clone producing the toxic light-chains, aiming to achieve a deep response that is predictive of improved OS. Alkylators and steroids are still a reasonable option for the treatment of amyloidosis. The combination of melphalan, prednisone, and colchicine was superior to colchicine in patients whose major manifestations of amyloid disease were other than cardiac or renal [66].

An Italian group reported the results of oral melphalan and dexamethasone in 46 patients with AL amyloidosis who were ineligible for ASCT; 67% achieved a hematologic response (CR in 33%) in a median time of 4.5 months. The median PFS and OS were 3.8 and 5.1 years, respectively [67]. Myelodysplasia became an increasingly important issue in patients treated with melphalan with a reported actuarial risk of myelodysplasia development at 10 years of 18% [68], and today melphalan is rarely used for more than 1 year.

A pivotal study showed the efficacy of melphalan and dexamethasone in 119 patients treated with melphalan and dexamethasone (40 mg, days 1–4), and 140 patients with advanced cardiac disease with an attenuated dexamethasone schedule (20 mg). The hematologic response rate was 76% in the first group and 51% in the second group, and the complete response rates were 31 and 12%, respectively. The median OS was 7.4 years in the first group and 20 months in second [69]. Bendamustine is currently being explored for its activity in AL amyloidosis [70].

Autologous Stem Cell Transplantation

Most AL amyloidosis patients are not eligible for ASCT due to their comorbidities. Early studies reported high mortality rates during ASCT for amyloid patients, but due to improved supportive care and careful patient selection, the mortality in ASCT has decreased significantly [71]. The reported early mortality rate (before day 100) was reduced to 1.1% when Mayo stage III patients were excluded from transplant [72].

The first issue in transplantation of AL amyloidosis patients is stem cell collection. The patients often accumulate fluids during filgrastim (granulocyte colony stimulating factor) mobilization [73] and fluid balance should be meticulously followed and maintained. The second issue in transplantation of AL amyloidosis patients is whether an induction before SCT improves outcomes. A single-center, prospective randomized trial evaluated the role of induction (two cycles of bortezomib and dexamethasone) versus no induction in 56 AL amyloidosis patients. OS at 24 months was 95% in the induction arm and 69% in the no induction arm, with higher rates of CR in the induction arm [74]. In another prospective study, 13 patients did not undergo induction whereas 12 patients did receive a bortezomib-based regimen. The median time to maximum hematologic response was reduced in the group that received bortezomib induction. The cardiac response rates were higher in patients pretreated with bortezomib and the 3-year PFS and OS were 66 and 73% [75]. In a study from the MDACC the type of induction therapy and its impact on the outcome of autologous hematopoietic stem cell transplantation in AL was evaluated in 128 patients. The patients were divided into 3 groups: no induction (20 patients), conventional chemotherapy-based induction (melphalan and steroids; 25 patients), and IMiD/proteasome inhibitor (PI)-based induction (83 patients). Overall, the hematological response on day 100 was highest in the IMiD/PI group, and organ response at 1 year was highest in the conventional chemotherapy-based induction. The 2-year PFS rates were 67, 56, and 73% in the no induction, CC, and IMiD/PI groups, respectively, and OS rates at 2 years were 73, 76, and 87%, respectively [76]. Mayo Clinic patients eligible for ASCT that have bone marrow plasma cells lower that 10% are sent directly to ASCT.

A randomized trial conducted by a French group compared HDM followed by ASCT with standard-dose melphalan plus high-dose dexamethasone in 100 patients with AL amyloidosis. The outcome of the ASCT arm was not superior to that of the standard-dose melphalan plus dexamethasone [77]. In a randomized trial, 89 patients received either ASCT or standard-dose melphalan plus high-dose dexamethasone. Patients who selected SCT were younger, more frequently had an ECOG score less than 2, had lower-stage amyloidosis, and had a lower incidence of cardiac amyloidosis. Patients receiving melphalan plus dexamethasone had a 3-year PFS of 29.1% and an OS of 58.8%. Patients undergoing SCT had a 3-year PFS of 51.7% and an OS rate of 83.6%. Similar hematologic responses were seen [78].

In a prospective multicenter phase II prospective phase II HOVON-41 study, the outcomes of 69 newly diagnosed patents receiving three courses of vincristine, doxorubicin, and dexamethasone followed by HDM and ASCT was evaluated. The median OS for the transplanted patients was 10 years. Treatment-related mortality was 12% and the author concluded that the regimen of vincristine, doxorubicin, and dexamethasone should not be used as an induction [79]. The median time to relapse after ASCT was 4 years and the median OS after hematological relapse was 4.4 years [80].

Proteasome Inhibitors

PIs are the backbone in the treatment of MM. Amyloid light-chain plasma cells are possibly more vulnerable to bortezomib than myeloma because of a distinct mechanism of action [81].

Bortezomib

Bortezomib is effective as a single agent and even more potent in combination with dexamethasone and alkylators. Bortezomib-based regimens have become a standard part of the initial treatment of AL amyloidosis in most centers.

Among 18 patients who received bortezomib and dexamethasone, 94% had a hematologic response (CR 44%). The median time to hematologic response was 0.9 months and the median time to organ response was 4 months. The side effects were manageable [82]. The addition of bortezomib to melphalan and prednisone resulted in a higher rate of complete responses, but this did not result in a survival benefit [83]. In a phase 1 dose escalation of 31 relapsed AL patients, doses of 1.6 mg/m^2 once weekly and 1.3 mg/m^2 twice weekly were used. Hematologic responses occurred in 50% (CR 20%). The median time to first response was 1.2 months. Once-weekly and twice-weekly bortezomib appear to be generally well tolerated [84].

A combination of bortezomib (1.5 mg/m^2 once weekly), cyclophosphamide (300 mg/m^2 orally weekly) and dexamethasone (40 mg weekly) was evaluated in 70 patients. The response rate was 94% (CR 71%). The time to response was 2 months and the treatment was well tolerated [85]. The same combination was reported in 230 patients treated frontline with CyBorD. Overall, the hematologic response rate was 60%. Cardiac and renal responses were 17 and 25%, respectively. Advanced cardiac stage III patients had lower response rates (42%) and a median OS of 7 months [86].

Carfilzomib

Carfilzomib (dosage 20/36 mg/m^2) seems to be effective but also toxic in this fragile patient population with a high rate of cardiac events. In a phase 1 trial, single-agent carfilzomib was tested in 12 patients with relapsed AL amyloidosis; 92% had received prior bortezomib. Overall, 78% achieved a hematologic response, and no organ responses have been observed. Seven patients had at least 1 grade ≥3 adverse event (AE), including cardiac events (4 patients), fatigue, diarrhea, and nausea. There have been 3 cardiac events, which were possibly drug related [87].

Ixazomib

Ixazomib has shown a surprisingly high efficacy with manageable toxicity and has received the Food and Drug Administration breakthrough therapy designation in 2014 for relapsed AL amyloidosis. Ixazomib was tested in a phase 1 study in 27 relapsed AL amyloid patients with a median of 3 prior therapies. Patients achieving less than a PR after 3 cycles also received dexamethasone of 40 mg. In the patients who received ixazomib of 4 mg, the overall response rate was 52%, which was higher in bortezomib-naive (100%) versus bortezomib-exposed patients (38%). Cardiac and renal responses were observed in 50 and 18% of patients, respectively. The most common drug-related AEs were diarrhea, nausea, fatigue, thrombocytopenia, peripheral neuropathy, and pyrexia. Drug-related grade 3 AEs were thrombocytopenia, diarrhea, and rash [88]. A phase 3 trial comparing ixazomib and dexamethasone versus standard treatment with no PIs is currently ongoing (NCT01659658). The results of the trial combining cyclophosphamide and dexamethasone for newly diagnosed AL amyloidosis are eagerly awaited (NCT03236792), as are the results of the ixazomib maintenance trial (NCT03618537).

Immunomodulatory Drugs

Immunomodulatory drugs are active agents in AL amyloidosis.

Thalidomide

Thalidomide in combination with other drugs has shown good clinical activity, but its use is accompanied by significant toxicity, especially neurotoxicity. In the first trial evaluating the outcomes of thalidomide use, 16 AL amyloidosis patients received a dose escalation of up to 300 mg/day, which caused high toxicity and therefore a high discontinuation rate [89]. Another report of a phase II trial that enrolled 12 patients also showed high toxicity and discontinuation rates [90].

Lenalidomide

The maximum tolerated dose is 15 mg/day since lenalidomide may aggravate heart failure and raise the NT-proBNP [91]. The toxicity and efficacy of single-agent lenalidomide were evaluated in 23 patients, 13 of whom were previously treated. If there was no hematologic response after 3 cycles, dexamethasone was added. There was limited activity of single-agent lenalidomide, but significant activity of the combination with dexamethasone [92].

The combination of melphalan and prednisone with lenalidomide (10 mg/day) was evaluated in 25 patients; 92% of the patients had cardiac involvement and 36% met the criteria for Mayo Clinic cardiac stage III disease. Ten patients died during the study, all within the first several months of treatment due to acute cardiac events. The overall hematological response was 58% and 1-year OS was 58% [93]. This regimen was toxic, ineffective, and did not alter survival outcomes for patients with high-risk cardiac disease.

Pomalidomide

Pomalidomide has activity in patients with relapsed AL amyloidosis with deep responses (VGPR or better), seen in a third of the patients. In a phase 2 trial, the safety and efficacy of pomalidomide and dexamethasone was tested in 28 patients that were previously exposed to bortezomib, alkylators, and other immunomodulatory drugs. Fifteen patients experienced grade 3/4 AE, with the most common being fluid retention and infection. A hematologic response was observed in 68% of patients (VGPR or better in 29%). The median OS and PFS were 26 and 16 months, respectively. The median time to response was 1 month [94].

Daratumumab

Daratumumab showed rapid and impressive responses in a case series of 25 previously treated AL patients who received the drug for 12 months (at the same schedule usually used for MM). Patients had received a median of 3 prior lines of therapy. The overall hematologic response rate was 76% (CR 36%, VGPR 24%), and the median time to response was 1 month. Therapy was well tolerated, even among the 72% of patients with cardiac AL involvement. Grade 1–2 infusion-related reactions (IRRs) occurred in 15 patients, but no grade 3 or 4 reactions were observed, suggesting that IRRs were less common in AL amyloid patients [95].

At the XVIth International Symposium on Amyloidosis in 2018, the results of a retrospective study of 41 relapsed or refractory AL amyloidosis patients receiving single agent daratumumab [20] and daratumumab combination therapy [21] were reported. After a median follow-up of 7.5 months, the hematologic response rate in 30 patients was 80%. A cardiac response was seen in 8 (33%) and renal response in 6 (32%) patients. The median PFS was 16.2 months and the median OS was not reached [96].

Antibodies

The discontinuation of the PRONTO trial was recently announced because the phase 2b study did not meet its endpoints. The phase 3 VITAL study was also discontinued based on a futility analysis. Several trials of antibodies use in AL amyloidosis are ongoing (NCT01777243, NCT02245867).

Venetoclax

Since t(11;14) is the most common cytogenetic abnormality in AL amyloidosis, it is logical that venetoclax will be important in the therapy of AL amyloidosis. In a case report of a patient with AL amyloidosis with t(11;14) who plateaued at a partial response with CyBorD therapy, the addition of venetoclax to bortezomib resulted in a complete response. The duration of response was short, and the κ-FLC began increasing within 3 months of stopping treatment along with serum creatinine. The patient quickly responded to venetoclax upon reintroduction [97]. A trial of venetoclax given at one of four escalating doses (100, 200, 400, or 800 mg/day) and dexamethasone is currently ongoing (NCT03000660).

Response Assessment

The evaluation of treatment response is based upon criteria both for the evaluation of the hematological response (e.g., light-chain levels) and organ response. The response criteria used today were validated in 2012. There are four levels of hematological responses: no response; PR requires the reduction of dFLC of 50%; VGPR requires dFLC <40 mg/L, and a CR that is defined as a normal FLC ratio and negative serum and urine immunofixation [98, 99].

Regarding organ response, at least a 30% reduction of NT-proBNP (if baseline was ≥650 ng/L with an absolute level of at least 300 ng/L) from baseline defines a cardiac response. Renal response criteria required the reduction of proteinuria by ≥50% without an increase in serum creatinine of 25% over baseline. Liver response is defined as a 50% decrease in the abnormal alkaline phosphatase value and a decrease in liver size radiographically of at least 2 cm. Nerve improvement seen on electromyography is rare [98]. Currently, organ response criteria do not consider the depth of response.

Conclusions

The importance of early recognition of AL amyloidosis cannot be overestimated. When a diagnosis of AL amyloidosis is made before the development of irreversible organ damage, patients can achieve much better outcomes. Once the AL amyloidosis is confirmed, patients should be evaluated for ASCT or clinical trials. Treatment options for patients with AL amyloidosis have broadened and continue to evolve with the addition of new drugs. Daratumumab and venetoclax are new therapeutic strategies that require further investigation.

Disclosure Statement

Dr. Gertz reports personal fees from Ionis/Akcea, personal fees from Alnylam, personal fees from Prothena, personal fees from Celgene, personal fees from Janssen, grants and personal fees from Spectrum, personal fees from Annexon, personal fees from Appellis, personal fees from Amgen, personal fees from Medscape, personal fees from Physicians Education Resource, personal fees for the Data Safety Monitoring board from Abbvie, personal fees from Research to Practice, speaker fees from Teva, speaker fees from Johnson and Johnson, speaker fees from Medscape, speaker fees from DAVA oncology, roles on the Advisory Board for Pharmacyclics and Advisory Board for Proclara outside the submitted work, royalties from Springer Publishing, and Grant Funding from Amyloidosis Foundation and International Waldenstrom Foundation; NCI SPORE MM SPORE 5P50 CA186781-04.

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