

## **Abstract**

**Introduction:** Systemic light-chain (AL) amyloidosis is an infiltrative disorder associated with an underlying plasma cells dyscrasia, in which monoclonal immunoglobulin light chains accumulate in an abnormal misfolded form as amyloid fibrils in the extracellular space. Symptoms and prognosis are governed by which organs are affected, and cardiac involvement is the major determinant of survival. Diagnosis requires demonstration of amyloid deposition and confirmation of the fibril protein type.

**Areas Covered:** This review will focus on the available treatments for systemic AL amyloidosis and on new drug targets and therapeutic approaches.

**Expert opinion:** At present, the choice of upfront treatment lies between autologous stem cell transplantation (ASCT) and combination chemotherapy. Chemotherapy agents include dexamethasone, melphalan, cyclophosphamide, thalidomide, bortezomib, lenalidomide, bendamustine in various combinations. Few randomized controlled trials have been performed in AL amyloidosis and treatment has been substantially influenced by clinical practice in myeloma. It has become clear that the best prospects of survival and preservation or improvement in amyloid related organ function require as near complete suppression as possible of the underlying hematological disorder. Future directions include therapies designed to target amyloid deposits directly, in particular anti-amyloid antibodies which are now well advanced in development and are showing great potential.

**Keywords:** immunoglobulin light-chain amyloidosis, screening, treatments, combination chemotherapy, stem cell transplantation, immunotherapeutic targeting, new frontiers.

|                    |  |
|--------------------|--|
| Article highlights | <ul style="list-style-type: none"> <li>• Systemic light-chain (AL) amyloidosis is an infiltrative disorder associated with an underlying plasma cells dyscrasia, in which monoclonal immunoglobulin light chains accumulate in an abnormal misfolded form as amyloid fibrils in the extracellular space and disrupt organ function.</li> <li>• The presenting clinical picture of patients with systemic AL amyloidosis is variable and non-specific. This is associated with a significant delay in the diagnosis, with 30% of patients presenting with a prognosis of less than 12 months. Screening of pre-symptomatic organ damage has the potential to change this.</li> <li>• The use of autologous stem cell transplantation (ACST) with high dose melphalan is associated with excellent and durable clonal responses, but only 20-25% of patients are currently eligible (low risk patients). Accurate patient selection, based on blood biomarkers, is crucial to reduce treatment related mortality. The intermediate and high risk patients should be considered for combination chemotherapy (melphalan-dexamethasone , bortezomib - cyclophosphamide - dexamethasone, bortezomib - melphalan -dexamethasone). Patients with relapsed or refractory disease should be considered for treatment with agents including bendamustine, lenalidomide and pomalidomide.</li> <li>• Patients achieving a hematologic complete response/very good partial response have the best chance to achieve organ responses, but stabilization or improvement in amyloidotic organ function occur also in a proportion of patients who achieved only partial hematologic responses. Tracking organ function very closely during chemotherapy is essential. Review after 3 cycles of treatment is suggested with dose increments, additional agents or alternative regimens in patients responding poorly.</li> <li>• New treatment strategies, directly targeting amyloid deposits and interfering with fibril formation, are currently well advanced in development and have the potential to reshape the treatment of AL amyloidosis.</li> </ul> |
|--------------------|--|

## 1. Introduction

Systemic amyloidosis is a rare disease caused by deposition of certain proteins that can misfold and aggregate in a highly characteristic fibrillar form within the extracellular space. All amyloid fibrils share an insoluble  $\beta$ -pleated sheet structure, and the various clinical amyloidosis disorders are classified according to the specific fibril precursor protein. Amyloid deposits can accumulate in many different organs and tissues, progressively disrupting their structure and function [1]. The most commonly involved organs are heart, kidneys, gastrointestinal tract, liver and peripheral and

autonomic nervous systems. The pattern of organ involvement is highly variable and determines the presenting clinical picture.

Immunoglobulin light chain (AL) amyloidosis is the most common type. This form is associated with a clonal plasma cell or, less frequently, B-lymphoid disorder, and AL amyloid fibrils are derived from monoclonal kappa or lambda light chains. AL amyloidosis rarely can occur in a localised form, typically confined to a single type of tissue, for example the skin, larynx, airways and urinary tract. Localised AL amyloidosis can usually be managed with local resection and has an excellent prognosis in most patients[2].

The second most common type is transthyretin amyloidosis (ATTR amyloidosis) in which the amyloid fibril protein is derived from transthyretin (TTR), an abundant plasma protein produced by the liver. ATTR amyloidosis encompasses wild type ATTR amyloidosis, previously known as senile systemic amyloidosis, in which wild type TTR is deposited as amyloid, and hereditary forms, in which genetically variant forms of TTR are implicated. Other types of hereditary amyloidosis are associated with to certain mutations in the genes for fibrinogen A  $\alpha$ -chain, apolipoproteins A1 and A2, lysozyme and gelsolin. In AA amyloidosis the fibril protein precursor is the acute phase reactant serum amyloid A protein; this type of amyloidosis is a rare complication of many chronic inflammatory disorders. The various subtypes of amyloidosis are listed in Table 1.

This review is focused on current strategies for the treatment of AL amyloidosis.

## **2. Clinical presentation and diagnosis**

The presenting clinical picture in systemic AL amyloidosis is extremely variable and dependent on the pattern of organ involvement. Symptoms are mostly non-specific including fatigue, dyspnoea, weight loss, edema, bleeding tendency, orthostatic hypotension and other features of autonomic or peripheral neuropathy. More specific features such as macroglossia and peri-orbital bruising are present in a third of cases [3]. The lack of specific clinical features frequently leads to delay in the diagnosis, and 30% of patients present with irreversible organ damage and a prognosis of less than 12 months[4] [5]. Use of biomarkers to detect pre-symptomatic organ damage has the potential to change this: serum N-terminal pro b-type natriuretic peptide (NT-proBNP) concentration has high diagnostic accuracy for the detection of cardiac involvement in AL amyloidosis [4]and albuminuria is an important marker for the detection of kidney infiltration. Biomarker screening therefore has a role in patients being followed up with monoclonal gammopathy of uncertain significance, about 2% of whom are thought to eventually develop systemic amyloidosis [4] (Figure 1).

Suspicion of AL amyloidosis requires confirmation through demonstration of amyloid in histological tissue sections of a biopsy taken from an affected organ or, less invasively, through abdominal fat or bone marrow aspiration. Amyloid deposits in tissue sections stain pink with Congo red dye and produce diagnostic apple-green birefringence when viewed under cross-polarized light (Figure 2)[6]. Fibril typing is then critical to determine appropriate therapy and is most widely performed through immunohistochemistry, which produces definitive results in about two-thirds of patients of AL amyloidosis [7]. Additional approaches include immuno-electron microscopy[8] and mass spectrometry, which can identify the amyloid protein in up to 98% of cases [9]. Detailed characterization of the underlying clonal hematological disorder is a further crucial step in planning the optimal treatment strategy. This includes serum and urine

electrophoresis and immunofixation, serum free light chain measurement, bone marrow biopsy and imaging for presence of myeloma related bone disease.

Baseline assessment of amyloid related organ dysfunction informs prognosis and selection of the most appropriate treatment. Echocardiography has long been used to assess cardiac involvement, but findings can be non-specific and other frequent co-morbidities such as hypertension can result in obscure interpretation. Cardiac magnetic resonance imaging (CMR) is the most sensitive and specific imaging modality for the diagnosis of cardiac amyloidosis [10, 11]. CMR, after the administration of contrast, shows a characteristic pattern of global subendocardial late gadolinium enhancement (LGE) coupled with abnormal myocardial and blood-pool gadolinium kinetics [11] (Figure 3). Bone scintigraphy tracers,  $^{99m}\text{Tc}$ -dicarboxypropane diphosphonate ( $^{99m}\text{Tc}$ -DPD) and  $^{99m}\text{Tc}$ -pyrophosphate ( $^{99m}\text{Tc}$ -PYP), localize with remarkable but unexplained sensitivity in cardiac ATTR amyloidosis. Visual scoring of cardiac uptake with  $^{99m}\text{Tc}$ -DPD scintigraphy according with *Perugini et al.* scale is routinely used in patients with ATTR amyloidosis [12, 13] and the combination of high degree of cardiac uptake (grade 2 or 3) in absence of serum or urine monoclonal proteins has been showed to be 100% specific for diagnosing of cardiac ATTR amyloidosis [14]. Cardiac localization of this radiotracer also occurs in a small portion of patients with AL amyloidosis, and hence endomyocardial biopsy may remain required in patients with positive cardiac scintigraphy who have a monoclonal gammopathy, since both AL and ATTR amyloidosis are differential diagnoses [15].

Formal evaluation of peripheral neuropathy and autonomic dysfunction may be useful in patients with a predominantly neuropathic phenotype. Serial quantification and monitoring of visceral amyloid deposits can be performed with  $^{125}\text{I}$  labeled serum amyloid P component (SAP)

scintigraphy [16]. This test allows the visualization and quantification of amyloid deposits within the liver, spleen, kidneys adrenals and bones, giving a baseline picture of the pattern of organ involvement as well as the ability to track changes over time in the specialized centres where the technique is available.

### **3. Prognosis and staging**

Serum troponin-T (TnT) and NT-proBNP measurements are currently the reference standard to stratify the prognosis of patients with AL amyloidosis, as described in the Mayo 2004 and 2012 staging systems[17-19]. The presence of zero, one, or two biomarkers above designated cutoff threshold defines stage I, II and III disease. Stage I, II and III are associated with median survival of 26.4, 10.5 and 3.5 months respectively [20]. The threshold values have been refined over the years and further modifications of the system have been to incorporate serum free light chain concentration and other clinical variables [21] [20, 22-24]. Patients with stage III disease with NT-proBNP above 8,500 pg/mL combined with a systolic blood pressure of <100 mmHg were found to have the poorest survival. Some reports have included high-sensitivity troponin T and I into prognostic models [24] [23]. The biggest limitation of this staging is the renal failure. For this reason is useful to consider a higher NT-proBNP cutoff when the estimated glomerular filtration rate (eGFR) is <60 mL/min/ 1.73 m<sup>2</sup> but for lower values (eGFR ≥ 15 ) the corresponding BNP cutoff should be preferred.[25]

Recently CMR derived measurements of cardiac amyloid burden have been explored as new variables adding additional independent prognostic power over the Mayo staging systems [11][26].

#### **4. Treatment of AL amyloidosis**

##### **4.1 Goals of therapy**

The mechanisms by which amyloid formation causes organ dysfunction are not completely understood, particularly in AL type. Physical and mechanical replacement of parenchymal tissue by amyloid deposits does not seem to fully explain the pathophysiology of AL amyloidosis, and a toxic effect, related to either a rapid rate of amyloid deposition or an inherent toxicity mediated directly by pre-fibrillary light chain protein aggregates, is thought to play an important role in the early mortality of patients with AL amyloidosis and cardiac infiltration. However debate continues on the nature of light chain toxicity, since this is not present in the absence of substantial amyloid deposits. Eradication in the shortest possible time of production of the AL amyloid fibril precursor protein (i.e. a haematological response measured in terms of reducing production of the aberrant clonal free light chains), minimization of treatment related toxicity and preservation of organ function are the primary goals of treatment[27, 28].

Achieving a haematological response translates into improved overall survival. Table 2 reports the consensus criteria for defining haematological and amyloidotic organ responses [28]. Although partial responses can be associated with some benefit, substantial 90-100% reduction in free light chain concentration is associated with the best clinical outcomes. According to consensus criteria

for hematologic response assessment [29] a very good partial response (VGPR) is defined as dFLC less than 40mg/L and is associated with an overall survival (OS) of 80-90% at 3 years [29]. A VGPR is currently considered the minimum goal of therapy.

Serial biomarkers are extremely important in evaluating a cardiac organ response. A reduction in NT-proBNP of 30% and 300 ng/L from baseline following completion of chemotherapy defines a cardiac response [27] [59]. In patients with cardiac amyloid infiltration, the lack of such a decrease in NT-proBNP among those who have not achieved a complete response (CR) supports consideration of further therapy to obtain a deeper hematologic response. Cardiac biomarkers are more sensitive than echocardiographic parameters of systo-diastolic function, but worsening renal failure or treatment with immunomodulatory drugs confound interpretation of these biomarkers, highlighting a need for other methods to specifically track the amyloid deposits.[30]

#### **4.2 Supportive Care**

Supportive treatment is a fundamental part of integrated clinical management. The aim is to maintain a good quality of life and palliate organ function. Supportive therapy for treatment of heart failure due to cardiac AL amyloidosis consists primarily of diuretics with fluid restriction and frequent adjustment according to daily weight measurements. Management of heart failure symptoms in cardiac AL can be very challenging since nephrotic syndrome, renal failure, and autonomic dysfunction often coexist. Frequent clinical assessment as well as measurement of electrolytes and creatinine are mandatory. A combination of loop diuretics and aldosterone antagonists are the mainstay of therapy, and caution is required regarding the use of other



standard heart failure medications. This requires the involvement of specialists familiar with the disease. Digoxin and calcium channel blockers have been associated with toxicity. Angiotensin converting enzyme inhibitors can precipitate hypotension in AL amyloidosis and the use of beta-blockers can cause or significantly exacerbate bradycardia, which has been shown to be a frequent terminal event in patients with cardiac AL amyloidosis. The alpha agonist midodrine can increase blood pressure in patients with orthostatic hypotension due to autonomic neuropathy.

Gastrointestinal symptoms can sometimes be due to bacterial overgrowth and respond to antimicrobial therapy, whilst metoclopramide, opioids or octreotide may relieve gastroparesis and diarrhea respectively. Sudden cardiac death is common in patients with cardiac AL amyloidosis.

Although implantable cardiac defibrillators can successfully terminate arrhythmias, evidence demonstrating their efficacy overall in prolonging survival remains lacking.[31]

Organ transplantation may be considered in patients with end stage amyloid related organ failure who would subsequently be eligible for autologous stem cell transplant (ASCT) or have achieved a complete clonal response to prior chemotherapy. The chief concerns surrounding organ transplantation are the systemic nature of the disease and the likelihood of recurrent amyloid deposition in the graft. The increasing availability of effective chemotherapy regimens has increased the proportion of patients in whom renal or occasionally cardiac transplantation can be considered.[32, 33]

#### ***4.3 Autologous Stem Cell Transplantation***

Following recognition that AL amyloidosis is caused by a clonal plasma cell disorder, treatments used for multiple myeloma have been applied and tested in AL amyloidosis. A significant advance

in myeloma treatment was autologous stem cell transplantation with high dose melphalan [34, 35] and this approach was adapted to patients with AL amyloidosis. The key differences between myeloma and amyloidosis patients soon became evident: AL patients have a lower tumor burden, but are significantly more fragile and often have multiple organ dysfunction. The mortality of the procedure in AL amyloidosis varies greatly with patient selection, but there is an overall 15% incidence of major complications during stem cell mobilization and collection, and a mortality rate of around 2-10%[37]. Appropriate patient selection is the key to reduction in morbidity and mortality and clinically significant cardiac amyloidosis is a contraindication.

Patients with AL amyloidosis can be in different categories of risks: low, intermediate, or high risk. Low risk patients (<20% of all cases) are potential candidates for ASCT[22, 38, 39]. Although a small randomised trial did not prove superiority of ASCT over standard chemotherapy[40], data from various non-randomised studies show excellent hematological response rates and long term survival. In one large center, 56% of patients achieved a VGPR [41], 44% of whom achieved a CR [42] that translated into improvement in organ function in three-quarters of cases, progression free survival longer than 8 years and median overall survival greater than 10 years[43]. ASCT can be performed relatively safely with strict patient selection, particularly using cardiac biomarkers with recent treatment-related mortality lower than 10%[38]. A strategy in which bortezomib is used for induction or consolidation seems to achieve the desired VGPR target in >90% of treated patients[44, 45]. ASCT is best undertaken in centers with particular experience in amyloidosis with the procedure.

#### **4.4 Combination Chemotherapy**

Most patients with AL amyloidosis can be classified to be of intermediate risk and are treated with less intensive combination chemotherapy regimens. Choice of treatment has grown substantially of late with development of many novel agents for myeloma, and few comparative clinical trials in amyloidosis have been performed. Recommendations for treatment and guidelines documents remains very much based on consensus of expert clinicians.

*Alkylators and steroid based regimens.* The first effective chemotherapy protocol for multiple myeloma was oral melphalan and prednisone, and a randomized clinical trial showed that this regimen had a small survival benefit for patients with AL amyloidosis. For more than 40 years alkylating agents and, more specifically, melphalan and corticosteroids have been considered the mainstay in treatment of AL amyloidosis [46]. The melphalan-dexamethasone (MDex) regimen is well tolerated with just 10-15% experiencing severe adverse events, mainly comprising fluid retention and cytopenias, and is associated with good haematological (67%) and organ (33%) response rates, with a third of patients achieving a complete clonal response. However the rates of hematological response to melphalan and prednisolone were relatively low and delayed allowing organ dysfunction to progress [27, 46]. MDex treatment remains an option for non-transplant eligible patients due to its low toxicity, simple oral formulation and eventual ability to produce good hematological responses even in patients with multiple organ involvement [47]. The role of MDex in patients with advanced cardiac disease is uncertain [48], since there is a strong rationale to obtain a more rapid response.

Multidrug regimens containing doxorubicin, vincristine and dexamethasone [49] or vincristine with multiple alkylator agents [50] were tested but did not show superiority over melphalan and dexamethasone. Pulsed dexamethasone has also been shown to be active in AL amyloidosis but high doses of dexamethasone cause considerable toxicity most commonly in patients with nephrotic syndrome and heart failure.

Bendamustine is an alkylator with a novel mechanism of action that has been used with steroids in relapsed/refractory disease [51]. Bendamustine needs to be explored earlier in the course of the disease.

*Immunomodulatory Agents.* The first generation agent thalidomide was poorly tolerated as a monotherapy and was associated with significant toxicity [52]. The combination of thalidomide and dexamethasone was more effective with overall clonal response rates of 48%. The median time to response was 3.6 months[53] but this was associated with significant toxicity. Dose adapted CTD (cyclophosphamide + thalidomide-dexamethasone), a risk adapted strategy based on patients clinical status, has been used with good and rapid hematologic responses[54] but relatively high toxicities[55]. This regime evolved as the standard of care in the UK before bortezomib was introduced in recent years.

Lenalidomide is an analogue of thalidomide with a superior toxicity profile in myeloma, and is now widely used in combination with dexamethasone (Len/dex) as a treatment for AL amyloidosis. Two phase II studies showed good haematological responses in 67% (n=24), with CR and partial response (PR) in 29% and 38% respectively.[56, 57]. Lenalidomide doses were often reduced because of myelosuppression. A Len/dex protocol has been tested in a small cohort of patients

refractory to thalidomide, bortezomib and alkylators, supporting their role in salvage treatment [58].

Complete response rates remain low with lenalidomide based regimes and addition of an alkylator have been tested in an attempt to improve the response rate [30, 59-62], but this incurred significant toxicity [27]. The most common adverse effects were myelosuppression and thromboembolism (hematologic side effects), fatigue and skin rash (non-hematologic side effects)[3][59].

A third generation Immunomodulatory imide drugs (IMiDs), pomalidomide, first used in myeloma patients refractory to lenalidomide, has been used in combination with dexamethasone [63] in refractory patients, showing promise for the use as salvage therapy.

IMiD's, although effective and an important part of the treatment in AL amyloidosis, are poorly tolerated compared with their use in multiple myeloma. During treatment with these agents an increase in cardiac biomarkers has been described [64] but this has not been associated with poor survival or renal deterioration.[30]

*Proteasome inhibitor based regimens.* Bortezomib, a reversible proteasome inhibitor, was developed with the aim of suppressing proliferation of proliferative malignant B-cell populations by inducing apoptosis [65]. Inhibition of proteasome function in plasma cells triggers apoptosis through stress-activated protein kinases and mitochondrial signaling pathways. Amyloidogenic plasma cells that produce misfolded light chains overloads the ubiquitin proteasome system and may be therefore more vulnerable to proteasome inhibitors. Clinical and Phase II clinical trial

experience have led to bortezomib combinations emerging as front line standard of care therapy in AL amyloidosis.

In the first study of bortezomib and dexamethasone on 18 patients, five had hematologic and organ progression with an average of 6.8 survival months [66]. A study conducted by National Amyloidosis Centre (UK) on 20 patients treated with bortezomib alone, revealed 80% haematological response rates and 30% organ responses. Data from multicentre retrospective analysis on 94 patients treated with bortezomib with or without dexamethasone showed high hematologic response rates (71%) that were achieved rapidly and were associated with consequent organ responses in 30% and one year survival of 76% [65]. A prospective phase I/II trial reported similar efficacy in patients with relapsed refractory AL amyloidosis which were divided in two groups based on once or twice weekly dosing [67].

A combination of bortezomib with cyclophosphamide and dexamethasone (CyBorD) is associated with very high response rates exceeding 90% for patients treated upfront, with 60% achieving CR or VGPR [68, 69]. This treatment therefore offers the hope of rapid and deep clonal responses and improvements in organ function, including the heart. However a recent study, on 230 patients treated frontline with CyBorD, showed 60% of hematologic response rate (43% VGPR), with cardiac and renal response reached in just in 17% and 25% respectively [70]. An ongoing randomised prospective trial is comparing MDex with bortezomib-melphalan-dexamethasone (BMDex). Novel proteasome inhibitors ixazomib and carfilzomib have higher specific activity than bortezomib that may be relevant clinically, and a different and potentially more favourable toxicity profile. A phase I study of oral ixazomib has been completed with good haematological response and tolerance and responses also in refractory patients [71]. A phase III trial is currently ongoing.

#### **4.5 IgM associated AL amyloidosis**

Six to seven percent of all patients with AL amyloidosis have an IgM secreting lymphoplasmacytic lymphoma as their underlying clonal hematologic disease [72, 73]. AL amyloidosis caused by IgM clones is a specific and distinct clinical entity characterized by more frequent involvement of the peripheral nervous system and lymph nodes and less cardiac involvement[74]. Combining NT-proBNP, Troponin T with liver involvement and presence of neuropathy gives in this population a better risk model [74]. Chemotherapy treatment should be directed toward the IgM clone. Single agent alkylators have shown limited efficacy. Regimes such as melphalan/dexamethasone and purine analogues are associated with good hematologic responses [72, 73]. Data for 250 patients with IgM related AL amyloidosis were recently published from a European multicentre study. Fifty-seven percent of patients achieved a hematological response (14% VGPR/CR) with median overall survival not reached for patients achieving VGPR/CR, 64 months for PR, and 28 months for nonresponders[20]. The data from this study confirmed that deeper hematological response translated into better outcomes, but deep hematological responses remain infrequent with currently available treatment.

#### **5. An approach to treatment**

Early diagnosis remains the holy grail in patients with AL amyloidosis since it allows the broadest range of therapeutic options at a stage where amyloidotic organ function has the best chance of being preserved. The treatment strategy is tailored patient by patient, and the choice is guided by factors including age, co-morbidities, performance status, organ involvement/dysfunction and relevant drug toxicities. Due to lack of clear evidence from randomized trials, patient preferences

must also be taken into account. The algorithm of Figure 4 presents the standard of care at our centre for patients treated outside clinical trials.

The choice of upfront treatment is between autologous stem cell transplantation (ASCT) and combination chemotherapy. Cardiac biomarkers have a central role in the selection of patients for ASCT. Younger patients with  $cTnT < 0.06$  ng/mL,  $NT\text{-}proBNP < 5000$  ng/L, good performance status, limited organ involvement and good renal function have  $< 5\%$  transplant-related mortality during ASCT [22, 75, 76]. This group of patients should be offered ASCT as a treatment choice. Patients with a bone marrow cell infiltrate  $> 10\%$  have a poor outcome [77] and benefit from induction treatment before ASCT [78]. Recently fluorescent in situ hybridization (FISH) abnormalities have been associated with different treatment outcomes, suggesting possible new approaches to guide treatment strategies [79, 80]. Borderline patients should be treated with a stem cell sparing regime as improved organ function may allow ASCT at a later date. In non neuropathic patients CyBorD or BMDex are becoming the regimens of choice. Treatment is best delivered in hospital with cardiac monitoring in patients with advanced cardiac involvement. Patients with neuropathy or those who develop it as an adverse effect of bortezomib can be offered melphalan/dexamethasone or lenalidomide/dexamethasone. Response reassessment after 3 cycles of treatment is key – patients with a poor response should be considered for either dose increments, additional agents eg thalidomide, or switching to an alternative regimen to improve response.

Amyloidotic organ responses occur most often among patients achieving a hematologic CR/VGPR, but a proportion of partial responders can also achieve an organ response, emphasizing the need to closely track the latter as well as the hematologic disorder. Lenalidomide and pomalidomide



based regimens or Bendamustine are useful in relapsed patients or in patients that are refractory to other treatments. The utility of alkylator-based regimes in patients relapsing after a novel agent is currently unclear.

No regimen has yet been proven to be superior or to reduce early cardiac deaths in patients that are very high-risk [20]. The rational desire for a rapid response underpins widespread adoption of bortezomib-based regimens, but superiority to other regimens has not been proven yet[81]. Improved outcomes in this subset are a major unmet medical need.

## **6. Enhancing regression and interfering with amyloidogenesis**

An attractive challenge in recent years has been to develop therapeutic antibodies that target amyloid deposits and promote their clearance. Mu11-1F4 is a chimeric antibody that binds to many AL fibrils [82] and is now in phase 1 clinical trial. A phase I/II study has been recently completed in patients with AL amyloidosis with another monoclonal antibody, NEOD001 (Onclave Therapeutics Limited, California), reporting good safety and tolerability and a suggestion of cardiac improvement; Of the 14 cardiac-evaluable patients, 8 (57%) met the criteria for cardiac responses and 6 (43%) has stable disease. A phase II expansion is ongoing and a global phase III randomized trial has lately been initiated[83]).

Serum amyloid P component (SAP) binds to all amyloid fibrils and there is in vitro evidence that SAP protects them from degradation by phagocytic cells and proteolytic enzymes. The (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) efficiently depletes SAP from the blood [84] but leaves some SAP in the amyloid deposits. SAP in the amyloid deposits can then be specifically targeted by therapeutic humanized monoclonal anti-SAP antibodies. A phase I trial involving 15 patients with amyloidosis has confirmed that this approach

can safely trigger clearance of amyloid deposits from the liver and some other sites including the kidney [85]. No serious adverse events were observed. A phase II study to investigate patients with cardiac amyloidosis is in planning.

The epigallocatechin gallate, a naturally derived phenol which is particularly present in the green tea, is able to interfere with the aggregation of the amyloidogenic proteins in vitro[86]. A case-control study of 11 patients treated with MDex associated with the consume of green tea, showed decreasing of symptoms and cardiac mass when compared to 22 historical controls[87]. The results are more promising for TTR cardiac amyloidosis[88], but his use on AL amyloidosis is now in phase 1 clinical trial [89].Furthermore there are new evidences that show how Epigallocatechin gallate antagonize bortezomib action in vitro [90].

Doxycycline, an antibiotic with similar structure to anthracycline 4'-iodo-4'-deoxy-doxorubicin (able to inhibit amyloidogenesis in vitro)[91, 92], has been shown to disrupt amyloid in a transgenic mice model and is able to counteract the proteotoxicity of amyloidogenic light chains. [93]Finally in a small retrospective case control study the addition of of doxycycline to chemotherapy improved survival of patients with stage II/IIIa. However patients in this study were matched based on the severity of the dis ease but not for chemotherapy regimen received.[94]



## **7. Conclusions**

Treatment of systemic AL amyloidosis has changed markedly in the last 10 years, as novel chemotherapy agents have become available. This has translated into improved overall survival, but challenges remain in advanced disease where the median survival is still very poor. FLC and blood biomarkers (troponin and brain natriuretic peptides) guide the selection and duration of treatment strategies. Treatments will continue to change, but the key target remains early diagnosis before end-stage organ failure has occurred. Broadening the amyloid-specific therapeutic landscape with immunotherapeutic targeting of amyloid deposits holds promise to transform outcomes in systemic AL amyloidosis.

## **8. Expert opinion**

AL amyloidosis is the most common type of systemic amyloidosis, but is rare overall and remains challenging to diagnose. The presenting clinical picture is variable and depends substantially on which organs are involved. Symptoms are often very non-specific. New diagnostic techniques have enabled earlier detection of disease and much improved characterization of organ involvement, but many patients continue to be diagnosed at a late stage when the function of one or more organs has become significantly impaired. The diagnosis requires confirmation of the presence of AL amyloid deposits, along with characterization of the underlying clonal hematological disorder.

Suppression of the AL amyloid light chain precursor protein (i.e. a haematological response) in the shortest possible time, minimization of treatment related toxicity and preservation of organ function are the primary goals of treatment. Baseline assessment of amyloid related organ dysfunction is required to stratify prognosis and tailor the most appropriate treatment for each patient. The presence and severity of cardiac involvement are the main determinants of outcome in patients with AL amyloidosis. Risk stratification using the serum cardiac biomarkers troponin and brain natriuretic peptides has refined treatment choices and has led to reduced morbidity and mortality, but selection of the optimal treatment for each patient remains complex and requires a multidisciplinary approach.

Few patients are too sick to embark on chemotherapy and choice of first line treatment lies between ASCT and combination chemotherapy. ASCT is associated with excellent and durable clonal responses in about half of patients and probably the best outcomes in terms overall survival, but meticulous patient selection, mainly based on the use of blood biomarkers, is key to

minimizing morbidity and mortality, and significant cardiac amyloidosis is an important contraindication. AL amyloidosis patients can be classified at diagnosis as at low, intermediate, or high risk. Low risk patients (<20% of all cases) are potential candidates for ASCT, whilst intermediate and high risk patients should be considered for combination chemotherapy.

Borderline patients should be treated with a stem cell sparing regime, since ASCT may remain a treatment option later on. In intermediate and low risk patients, novel agent based chemotherapy, especially including bortezomib, has greatly improved the speed and depth of hematologic responses and is being explored as an adjunct before and after ASCT. Bendamustine, lenalidomide and pomalidomide are valuable therapies for patients whose clonal disease has relapsed or is refractory.

Early mortality among patients with advanced disease remains a major challenge, and nearly 25% of all patients still die of complications within a few months of diagnosis. Patients achieving a hematologic CR/VGPR have the best chance to achieve organ responses, but stabilization or improvement in amyloidotic organ function does occur in a proportion of patients with only partial hematologic responses, emphasizing the need to track organ function closely in all cases as a guide to the need for ongoing therapy. Frequent assessments of haematological response are required: our practice is to conduct a broad review after 3 cycles of treatment, and patients with a poor response are considered for dose increments, additional agents or alternative regimens.

Future directions include therapies that directly target amyloid deposits or inhibit fibrillogenesis. These molecules are now well advanced in development and have the potential to reshape the treatment of AL amyloidosis when used in conjunction with the many new chemotherapy agents that are already finding their place in clinical practice.

## **Declaration of Interest section**

No conflict of interest to disclose.

## Bibliography

1. Kyle, R.A. et al., *Primary systemic amyloidosis: clinical and laboratory features in 474 cases*. Semin Hematol, 1995. **32**(1): p. 45-59.
2. Biewend, M. L., et al., *The spectrum of localized amyloidosis: a case series of 20 patients and review of the literature*. Amyloid, 2006. **13**(3): p. 135-42.
3. Mahmood, S., et al., *Update on treatment of light chain amyloidosis*. Haematologica, 2014. **99**(2): p. 209-21.
4. Merlini, G., et al., *Systemic light chain amyloidosis: an update for treating physicians*. Blood, 2013. **121**(26): p. 5124-30.
5. Merlini, G. et al., *Light chain amyloidosis: the heart of the problem*. Haematologica, 2013. **98**(10): p. 1492-5.
6. Picken, M.M. et al., *Amyloidosis-where are we now and where are we heading?* Arch Pathol Lab Med, 2010. **134**(4): p. 545-51.
7. Schonland, S.O., et al., *Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients*. Blood, 2012. **119**(2): p. 488-93.
8. Fernandez de Larrea, C., et al., *A practical approach to the diagnosis of systemic amyloidoses*. Blood, 2015. **125**(14): p. 2239-44.



9. Gilbertson, J.A., et al., *A comparison of immunohistochemistry and mass spectrometry for determining the amyloid fibril protein from formalin-fixed biopsy tissue*. *J Clin Pathol*, 2015. **68**(4): p. 314-7.
10. Maceira, A.M., et al., *Cardiovascular magnetic resonance in cardiac amyloidosis*. *Circulation*, 2005. **111**(2): p. 186-93.
11. Fontana, M., et al., *Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis*. *Circulation*, 2015. **132**(16): p. 1570-9.
12. Rapezzi, C., et al., *Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis*. *JACC Cardiovasc Imaging*, 2011. **4**(6): p. 659-70.
13. Rapezzi, C., et al., *Usefulness of 99mTc-DPD scintigraphy in cardiac amyloidosis*. *J Am Coll Cardiol*, 2008. **51**(15): p. 1509-10; author reply 1510.
14. Gillmore, J.D., et al., *Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis*. *Circulation*, 2016. **133**(24): p. 2404-12.
15. Dispenzieri, A., et al., *International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders*. *Leukemia*, 2009. **23**(2): p. 215-24.
16. Hawkins, P.N., et al., *Evaluation of systemic amyloidosis by scintigraphy with 123I-labeled serum amyloid P component*. *N Engl J Med*, 1990. **323**(8): p. 508-13.

17. Dispenzieri, A., et al., *Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis*. J Clin Oncol, 2004. **22**(18): p. 3751-7.
18. Kumar, S., et al., *Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements*. J Clin Oncol, 2012. **30**(9): p. 989-95.
19. Dispenzieri, A., et al., *Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation*. Blood, 2004. **104**(6): p. 1881-7.
20. Wechalekar, A.D., et al., *A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis*. Blood, 2013. **121**(17): p. 3420-7.
21. *Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 20-1998. A 53-year-old man with cardiac amyloidosis and a left pulmonary mass*. N Engl J Med, 1998. **338**(26): p. 1905-13.
22. Gertz, M.A., et al., *Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis*. Bone Marrow Transplant, 2013. **48**(4): p. 557-61.
23. Kristen, A.V., et al., *Assessment of disease severity and outcome in patients with systemic light-chain amyloidosis by the high-sensitivity troponin T assay*. Blood, 2010. **116**(14): p. 2455-61.

24. Palladini, G., et al., *The combination of high-sensitivity cardiac troponin T (hs-cTnT) at presentation and changes in N-terminal natriuretic peptide type B (NT-proBNP) after chemotherapy best predicts survival in AL amyloidosis*. Blood, 2010. **116**(18): p. 3426-30.
25. Palladini, G., et al., *Best use of cardiac biomarkers in patients with AL amyloidosis and renal failure*. Am J Hematol, 2012. **87**(5): p. 465-71.
26. Banyersad, S.M., et al., *T1 mapping and survival in systemic light-chain amyloidosis*. Eur Heart J, 2015. **36**(4): p. 244-51.
27. Comenzo, R.L., et al., *Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis*. Leukemia, 2012. **26**(11): p. 2317-25.
28. Gertz, M.A., et al., *Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response*. Haematologica, 2007. **92**(10): p. 1415-8.
29. Palladini, G., et al., *New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes*. J Clin Oncol, 2012. **30**(36): p. 4541-9.
30. Kastritis, E., et al., *A phase 1/2 study of lenalidomide with low-dose oral cyclophosphamide and low-dose dexamethasone (RdC) in AL amyloidosis*. Blood, 2012. **119**(23): p. 5384-5390.

31. Lin, G., et al., *Implantable cardioverter defibrillators in patients with cardiac amyloidosis*. J Cardiovasc Electrophysiol, 2013. **24**(7): p. 793-8.
32. Elnegouly, M., et al., *Liver transplantation followed by autologous stem cell transplantation for acute liver failure caused by AL amyloidosis. Case report and review of the literature*. Ann Hepatol, 2016. **15**(4): p. 592-7.
33. Grogan, M., et al., *Long term outcomes of cardiac transplant for immunoglobulin light chain amyloidosis: The Mayo Clinic experience*. World J Transplant, 2016. **6**(2): p. 380-8.
34. Sanchorawala, V., et al., *Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation*. Blood, 2007. **110**(10): p. 3561-3563.
35. Dispenzieri, A., et al., *Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival*. J. Clin. Oncol., 2001. **19**(14): p. 3350-3356.
36. Gertz, M., et al., *Troponin T level as an exclusion criterion for stem cell transplantation in light-chain amyloidosis*. Leuk Lymphoma, 2008. **49**(1): p. 36-41.
37. Milani P, P., et al., *Melphalan and dexamethasone vs Bortezomib, melphalan and dexamethasone in AL amyloidosis: a matched comparison*. XIVth Myeloma Workshop, 2013.

38. Gertz, M.A., et al., *Trends in day 100 and 2-year survival after auto-SCT for AL amyloidosis: outcomes before and after 2006*. Bone Marrow Transplant, 2011. **46**(7): p. 970-5.
39. Comenzo, et al., *Autologous stem cell transplantation for primary systemic amyloidosis*. Blood, 2002. **99**(12): p. 4276-82.
40. Jaccard, A., et al., *High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis*. N Engl J Med, 2007. **357**(11): p. 1083-93.
41. Santhorawala, V., et al., *Serum free light-chain responses after high-dose intravenous melphalan and autologous stem cell transplantation for AL (primary) amyloidosis*. Bone Marrow Transplant, 2005. **36**(7): p. 597-600.
42. Skinner, M., et al., *High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study*. Ann Intern Med, 2004. **140**(2): p. 85-93.
43. Cibeira, M.T., et al., *Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients*. Blood, 2011. **118**(16): p. 4346-52.
44. Landau, H., et al., *Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis*. Leukemia, 2013. **27**(4): p. 823-8.
45. Santhorawala, V., et al., *Induction Therapy with Bortezomib Followed by Bortezomib-High Dose Melphalan and Stem Cell Transplantation for Light Chain*

- Amyloidosis: Results of a Prospective Clinical Trial*. Biol Blood Marrow Transplant, 2015. **21**(8): p. 1445-51.
46. Kyle, R.A., et al., *A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine*. N Engl J Med, 1997. **336**(17): p. 1202-7.
47. Palladini, G., et al., *Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis*. Blood, 2007. **110**(2): p. 787-8.
48. Lebovic, D., et al., *Predictors of survival in patients with systemic light-chain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone*. Br. J. Haematol., 2008. **143**(3): p. 369-373.
49. Wardley, A.M., et al., *The treatment of nephrotic syndrome caused by primary (light chain) amyloid with vincristine, doxorubicin and dexamethasone*. Br J Cancer, 1998. **78**(6): p. 774-6.
50. Gertz, M.A., et al., *Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis*. J Clin Oncol, 1999. **17**(1): p. 262-7.
51. Palladini, G., et al., *Treatment of AL Amyloidosis with Bendamustine*. Blood, 2012. **120**(21): p. 120.

52. Seldin, D.C., et al., *Tolerability and efficacy of thalidomide for the treatment of patients with light chain-associated (AL) amyloidosis*. Clin Lymphoma, 2003. **3**(4): p. 241-6.
53. Palladini, G., et al., *The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL)*. Blood, 2005. **105**(7): p. 2949-51.
54. Wechalekar, A.D., et al., *Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis*. Blood, 2007. **109**(2): p. 457-464.
55. Lane, T., et al., *ALchemy - A Large Prospective 'Real World' Study of Chemotherapy in AL Amyloidosis*. Blood, 2011. **118**(21): p. 992.
56. Santhorawala, V., et al., *Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial*. Blood, 2007. **109**(2): p. 492-496.
57. Dispenzieri, A., et al., *The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis*. Blood, 2007. **109**(2): p. 465-470.
58. Palladini, G., et al., *Salvage therapy with lenalidomide and dexamethasone in patients with advanced AL amyloidosis refractory to melphalan, bortezomib, and thalidomide*. Ann Hematol, 2012. **91**(1): p. 89-92.
59. Dinner, S., et al., *Lenalidomide, melphalan and dexamethasone in an immunoglobulin light chain amyloidosis patient population with high rates of advanced cardiac involvement*. Haematologica.

60. Palladini, G., et al., *A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis*. *Haematologica*, 2013. **98**(3): p. 433-6.
61. Kumar, S.K., et al., *Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial*. *Blood*, 2012. **119**(21): p. 4860-4867.
62. Moreau, P., et al., *Lenalidomide in combination with melphalan and dexamethasone in patients with newly diagnosed AL amyloidosis: a multicenter phase 1/2 dose-escalation study*. *Blood*, 2010. **116**(23): p. 4777-82.
63. Dispenzieri, A., et al., *Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis*. *Blood*, 2012. **119**(23): p. 5397-5404.
64. Tapan, U., et al., *Increases in B-type natriuretic peptide (BNP) during treatment with lenalidomide in AL amyloidosis*. *Blood*, 2010. **116**(23): p. 5071-5072.
65. Kastritis, E., et al., *Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis*. *J Clin Oncol*, 2010. **28**(6): p. 1031-7.
66. Kastritis, E., et al., *Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone*. *Haematologica*, 2007. **92**(10): p. 1351-8.
67. Reece, D.E., et al., *Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study*. *Blood*, 2011. **118**(4): p. 865-873.



68. Venner, C.P., et al., *Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival*. *Blood*, 2012. **119**(19): p. 4387-90.
69. Mikhael, J.R., et al., *Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis*. *Blood*, 2012. **119**(19): p. 4391-4.
70. Palladini, G., et al., *A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis*. *Blood*, 2015. **126**(5): p. 612-5.
71. Sancharawala V, et al.,, *MLN9708, an investigational oral proteasome inhibitor (PI) in relapsed or refractory light-chain (AL) Amyloidosis*. 2013.
72. Terrier, B., et al., *The Clinical Spectrum of IgM-Related Amyloidosis: A French Nationwide Retrospective Study of 72 Patients*. *Medicine*, 2008. **87**(2): p. 99-109  
10.1097/MD.0b13e31816c43b6.
73. Wechalekar, A.D., et al., *AL amyloidosis associated with IgM paraproteinemia: clinical profile and treatment outcome*. *Blood*, 2008. **112**(10): p. 4009-4016.
74. Sachchithanatham, S., et al., *European Collaborative Study Defining Clinical Profile Outcomes and Novel Prognostic Criteria in Monoclonal Immunoglobulin M-Related Light Chain Amyloidosis*. *J Clin Oncol*, 2016. **34**(17): p. 2037-45.
75. Palladini, G. et al., *Transplantation vs. conventional-dose therapy for amyloidosis*. *Curr. Opin. Oncol.*, 2011. **23**(2): p. 214-220.

76. Dispenzieri, A., et al., *Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study*. *Blood*, 2004. **103**(10): p. 3960-3.
77. Kourelis, T.V., et al., *Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis*. *J Clin Oncol*, 2013. **31**(34): p. 4319-24.
78. Hwa YL, et al., *Impact of Bone Marrow Plasmacytosis on Outcome in Patients with AL Amyloidosis Following Autologous Stem Cell Transplant*. *Blood*, 2015. **126:3177**.
79. Bochtler, T., et al., *Gain of chromosome 1q21 is an independent adverse prognostic factor in light chain amyloidosis patients treated with melphalan/dexamethasone*. *Amyloid*, 2014. **21**(1): p. 9-17.
80. Bochtler, T., et al., *Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens*. *J Clin Oncol*, 2015. **33**(12): p. 1371-8.
81. Venner, C.P., et al., *A matched comparison of cyclophosphamide, bortezomib and dexamethasone (CVD) versus risk-adapted cyclophosphamide, thalidomide and dexamethasone (CTD) in AL amyloidosis*. *Leukemia*, 2014. **28**(12): p. 2304-10.
82. O'Nuallain, B., et al., *Diagnostic and therapeutic potential of amyloid-reactive IgG antibodies contained in human sera*. *J Immunol*, 2006. **176**(11): p. 7071-8.

83. Gertz, M.A., et al., *First-in-Human Phase I/II Study of NEOD001 in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction*. J Clin Oncol, 2016. **34**(10): p. 1097-103.
84. Gillmore, J.D., et al., *Sustained pharmacological depletion of serum amyloid P component in patients with systemic amyloidosis*. Br J Haematol, 2010. **148**(5): p. 760-7.
85. Richards, D.B., et al., *Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component*. N Engl J Med, 2015. **373**(12): p. 1106-14.
86. Stefani, M. et al., *Beneficial properties of natural phenols: highlight on protection against pathological conditions associated with amyloid aggregation*. Biofactors, 2014. **40**(5): p. 482-93.
87. Mereles, D., et al., *Effects of the main green tea polyphenol epigallocatechin-3-gallate on cardiac involvement in patients with AL amyloidosis*. Clin Res Cardiol, 2010. **99**(8): p. 483-90.
88. Aus dem Siepen, F., et al., *Extracellular remodeling in patients with wild-type amyloidosis consuming epigallocatechin-3-gallate: preliminary results of T1 mapping by cardiac magnetic resonance imaging in a small single center study*. Clin Res Cardiol, 2015. **104**(8): p. 640-7.
89. *ClinicalTrials.gov: A trial for the treatment of cardiac AL-amyloidosis with the green tea compound epigallocatechin-3-gallate (TAME-AL) (TAME-AL)*

<https://clinicaltrials.gov/ct2/show/NCT02015312?term=NCT02015312&rank=1>.

November 18, 2013.

90. Golden, E.B., et al., *Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors*. *Blood*, 2009. **113**(23): p. 5927-37.
91. Merlini, G., et al., *Interaction of the anthracycline 4'-iodo-4'-deoxydoxorubicin with amyloid fibrils: inhibition of amyloidogenesis*. *Proc Natl Acad Sci U S A*, 1995. **92**(7): p. 2959-63.
92. Gianni, L., et al., *New drug therapy of amyloidoses: resorption of AL-type deposits with 4'-iodo-4'-deoxydoxorubicin*. *Blood*, 1995. **86**(3): p. 855-61.
93. Diomedea, L., et al., *A Caenorhabditis elegans-based assay recognizes immunoglobulin light chains causing heart amyloidosis*. *Blood*, 2014. **123**(23): p. 3543-52.
94. Wechalekar A, et al., *Oral Doxycycline Improves Outcomes of Stage III AL Amyloidosis - a Matched Case Control Study*. *Blood*, 2015. **126**(21). **Abstract 732**.

**Table 1:** Most common types of systemic amyloidosis.

| <b>TYPE</b>  | <b>Abbreviation</b>         | <b>Precursor and pathogenesis</b>                                      | <b>Site of Synthesis</b>          | <b>Organs Involved</b>  |
|--|-----------------------------|--|-----------------------------------|---|
| <b>Immunoglobulin Light Chain Amyloidosis</b>      | AL                          | Monoclonal Light chain (primary)                                       | Bone marrow or serum B cell clone | Heart, kidneys, GI tract, liver, autonomic and peripheral nerves, soft tissue |
| <b>Systemic AA (reactive systemic amyloidosis)</b> | AA                          | Serum amyloid A protein (increased production in chronic inflammation) | Liver                             | Kidneys, GI tract, spleen, liver, autonomic nerves                            |
| <b>Hereditary transthyretin Amyloidosis</b>        | ATTRm (hereditary mutation) | More than 100 mutation known (hereditary)                              | Liver                             | Peripheral and autonomic nerves, heart, leptomeninges, eye                    |
| <b>Wild type transthyretin Amyloidosis</b>         | (ATTRwt)                    | Wild type Transthyretin  | Liver                             | Heart   |
| <b>Fibrinogen Amyloidosis</b>                      | AFib                        | Fibrinogen A $\alpha$ -chain (hereditary)                              | Liver                             | Kidneys   |
| <b>Apolipoprotein A1</b>                           | AApoA1                      | Apolipoprotein A1 (hereditary)   | Liver, intestine                  | Heart, liver, kidneys, skin, larynx   |
| <b>Leukocyte chemotactic factor 2</b>              | ALECT2                      | Leukocyte chemotactic factor 2   | Liver                             | Kidneys, liver, spleen, lung  |

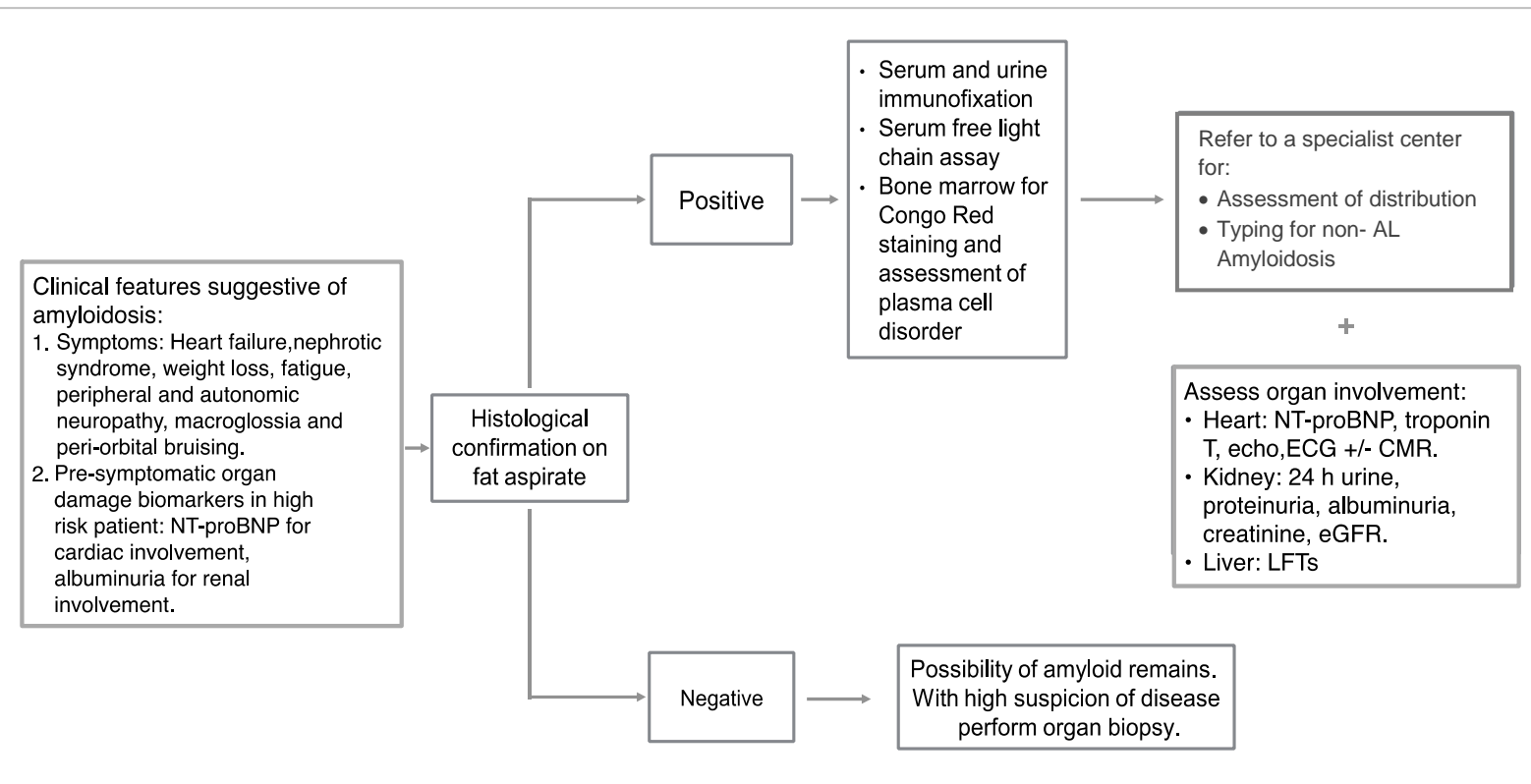
GI tract, gastro-intestinal tract.

**Table 2:** Consensus Hematologic and Organs Response in AL amyloidosis [27]

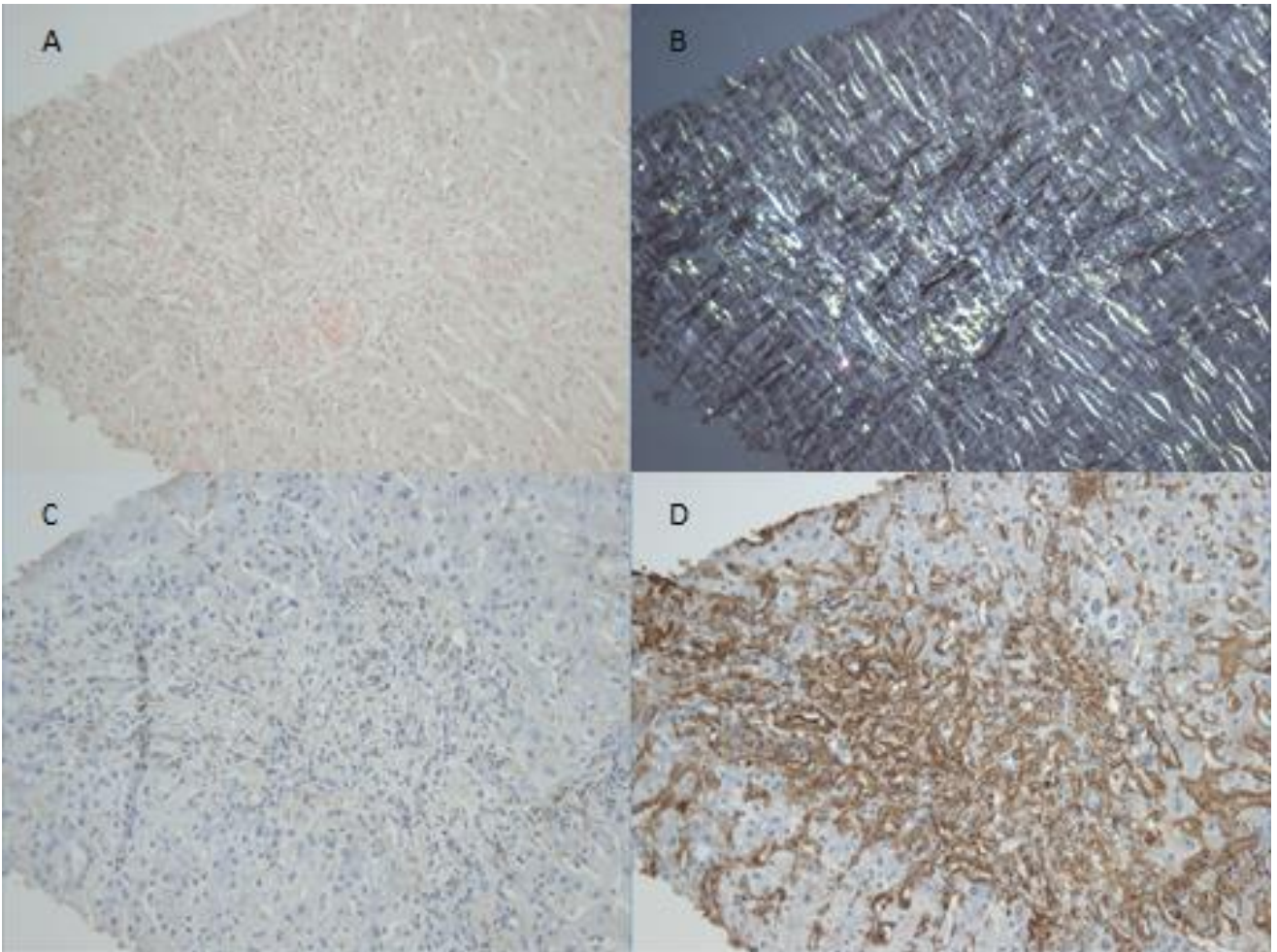
| RESPONSE TYPE                 |                                   | CRITERIA   |
|-------------------------------|-----------------------------------|--|
| <b>Hematological response</b> | Complete response(CR)             | Negative serum and urine immunofixation and normal $\kappa/\lambda$ ratio  |
|                               | Very good partial response (VGPR) | dFLC < 40mg/L  |
|                               | Partial response (PR)             | dFLC reduction $\geq$ 50%  |
|                               | No response (NR)                  | A less than 50% response in dFLC   |
| <b>Organ response</b>         | Heart                             | NT-proBNP response (>30% and >300 ng/l decrease in patients with baseline NT-proBNP $\geq$ 650 ng/l) or NYHA class response ( $\geq$ 2 class decrease in subjects with baseline NYHA class 3 or 4) |
|                               | Kidney                            | 50% decreased urinary protein excretion in 24-hour without a reduction in eGFR $\geq$ 25% or an increase in serum creatinine $\geq$ 0.5 mg/dL  |
|                               | Liver                             | 50% decreased alkaline phosphatase value. Liver size decrease >2 cm  |
|                               | Peripheral nervous system         | Improvement in electromyogram nerve conduction velocity  |

dFLC – difference between involved and uninvolved free light chains.

**Figure 1:** The algorithm of standard of care for patients treated outside clinical trials



**Figure 2:** Typical diagnostic amyloid findings on histological examination: Congo red staining (A), apple-green birefringence under cross-polarized light (B). Immunostaining with antibodies to kappa light chains (negative) (C) and with antibodies to lambda (positive) (D)





**Figure 3:** Main diagnostic techniques for cardiac AL amyloidosis. ECG, showing low voltages in the limb leads (A); echocardiography, showing concentric left ventricular hypertrophy and biatrial dilatation (B); late gadolinium enhancement image by cardiac magnetic resonance showing the typical subendocardial late gadolinium enhancement coupled with abnormal blood pool gadolinium kinetics (C); non contrast T1 map by cardiac magnetic resonance showing elevated native myocardial T1 (D).

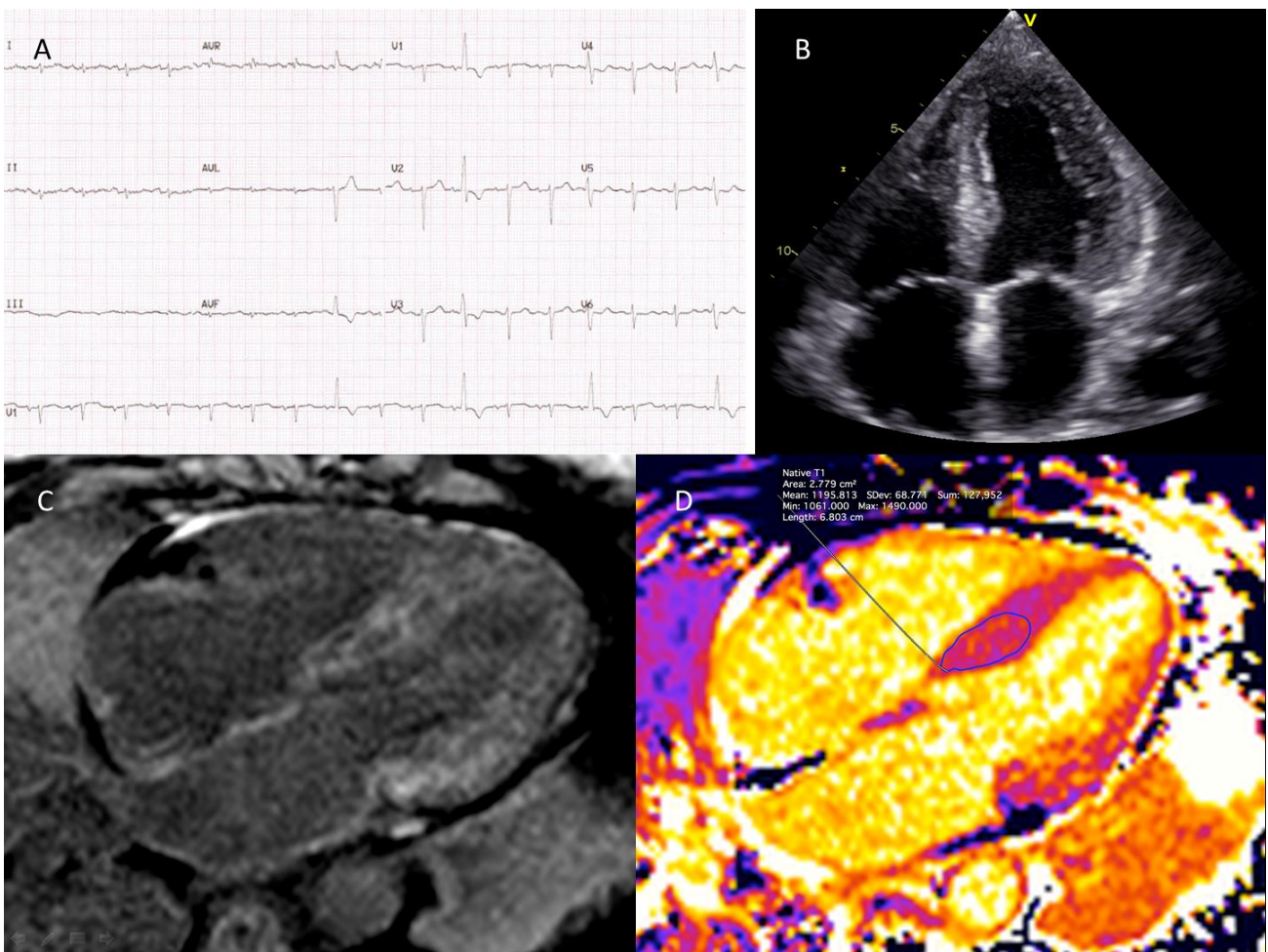
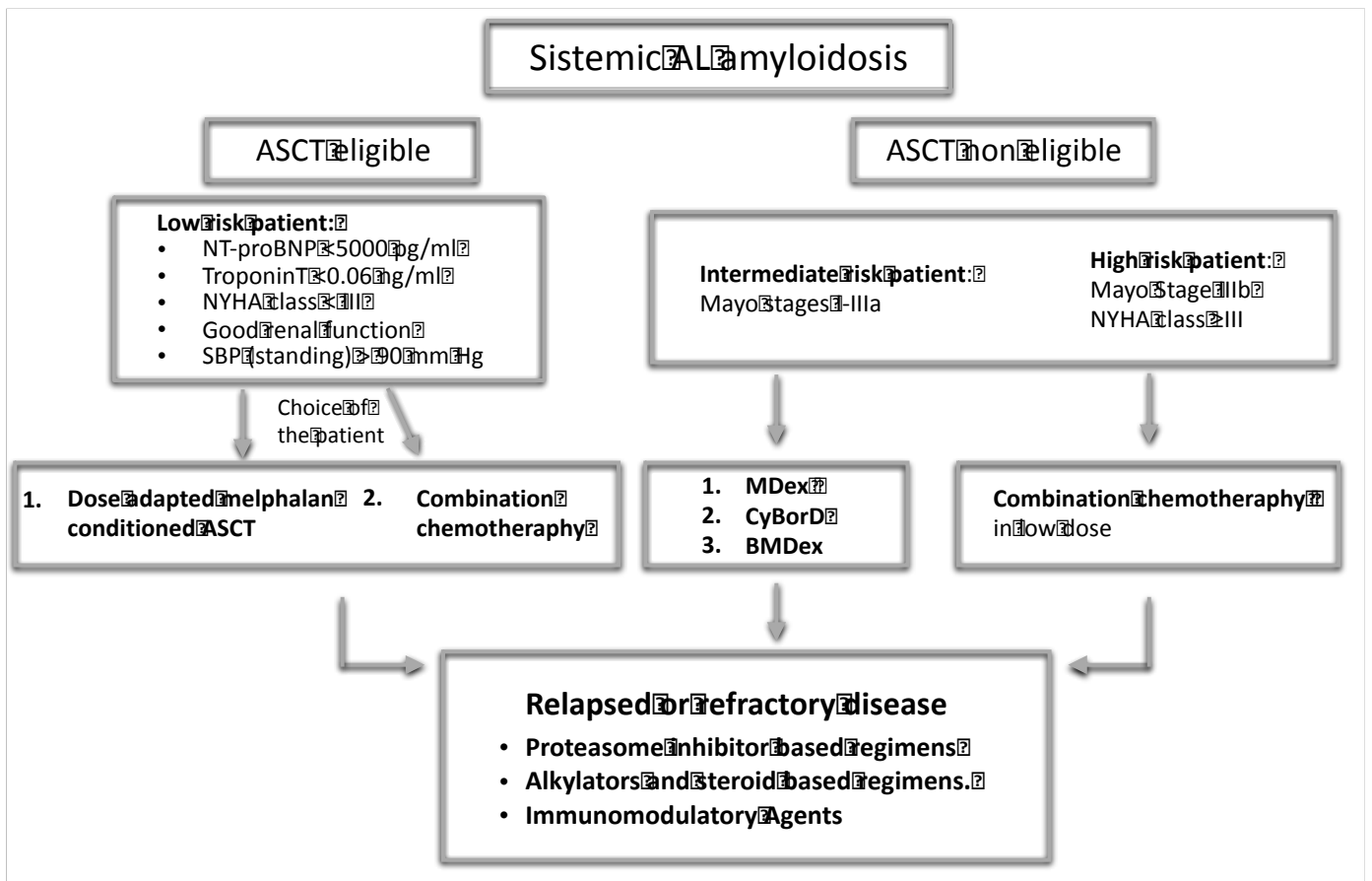


Figure 4. Treatment algorithm in systemic AL amyloidosis patients.



ASCT, autologous stem cell transplantation; NT-proBNP, amino-terminal proatriuretic peptide type-B; NYHA, New York Heart Association; SBP, systolic blood pressure.; MDex, melphalan /dexamethasone; BDex, bortezomib dexamethasone; CyBorD, cyclophosphamide / bortezomib /dexamethasone; BMDex, bortezomib / melphalan / dexamethasone.