



**Review Article**

**Light Chain Amyloidosis**

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**Competing interests:** The authors have declared that no competing interests exist.

**Abstract.** Light chain (AL) amyloidosis is caused by a usually small plasma-cell clone that is able to produce the amyloidogenic light chains. They are able to misfold and aggregate, deposit in tissues in the form of amyloid fibrils and lead to irreversible organ dysfunction and eventually death if treatment is late or ineffective. Cardiac damage is the most important prognostic determinant. The risk of dialysis is predicted by the severity of renal involvement, defined by the baseline proteinuria and glomerular filtration rate, and by the response to therapy. The specific treatment is chemotherapy targeting the underlying plasma-cell clone. It needs to be risk-adapted, according to the severity of cardiac and/or multi-organ involvement. Autologous stem cell transplant (preceded by induction and/or followed by consolidation with bortezomib-based regimens) can be considered for low-risk patients (~20%). Bortezomib combined with alkylators is used in the majority of intermediate-risk patients, and with possible dose escalation in high-risk subjects. Novel, powerful anti-plasma cell agents were investigated in the relapsed/refractory setting, and are being moved to upfront therapy in clinical trials. In addition, the use of novel approaches based on antibodies targeting the amyloid deposits or small molecules interfering with the amyloidogenic process gave promising results in preliminary studies. Some of them are under evaluation in controlled trials. These molecules will probably add powerful complements to standard chemotherapy. The understanding of the specific molecular mechanisms of cardiac damage and the characteristics of the amyloidogenic clone are unveiling novel potential treatment approaches, moving towards a cure for this dreadful disease.

**Keywords:** amyloidosis, light chains, diagnosis, therapy, response.

**Citation:** Milani P., Merlini G., Palladini G. Light Chain Amyloidosis. *Mediterr J Hematol Infect Dis* 2018, 10(1): e2018022, DOI: <http://dx.doi.org/10.4084/MJHID.2018.022>

**Published:** March 1, 2018

**Received:** January 10, 2018

**Accepted:** February 5, 2018

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**Introduction.** Immunoglobulin light chain (AL) amyloidosis is the most common form of systemic amyloidosis, accounting for approximately 70% of all subjects suffering from these diseases.<sup>1</sup> It is caused by a plasma cell clone that infiltrates the bone marrow by less than 10% in half of the patients. Despite its relatively small size, the clone

can set off a devastating multi-organ damage caused by the monoclonal light chain.<sup>2</sup> The amyloidogenic light chain misfolds and aggregates, depositing in tissues in the form of amyloid fibrils.<sup>3</sup> All organs, except for the central nervous system, can be affected by this process, that leads to irreversible organ dysfunction and

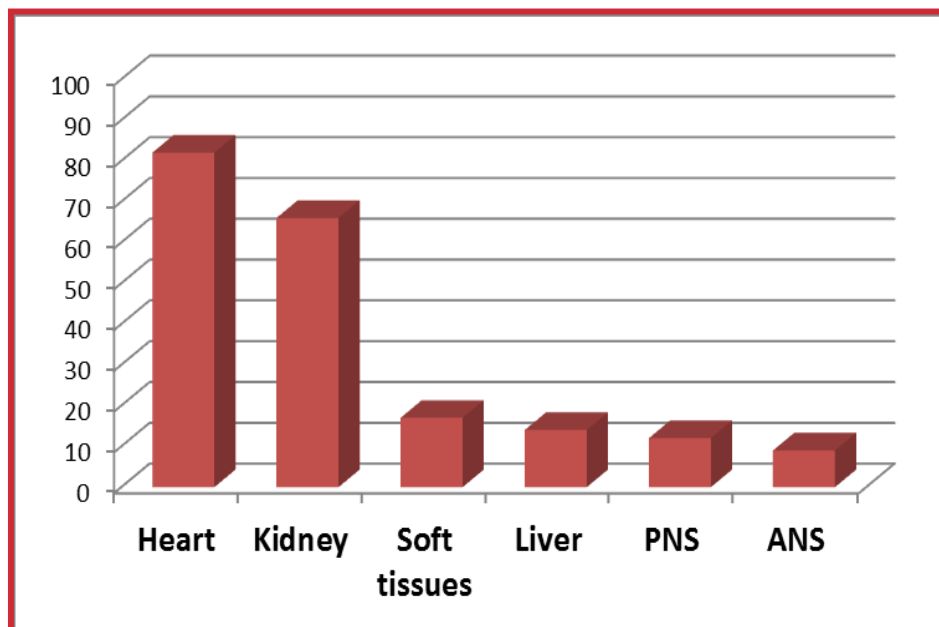
death if unrecognized or treated ineffectively.<sup>3</sup> In the last 15 years, we have made substantial progress in understanding the biology of the amyloid plasma cell clone and the mechanisms of organ damage. Moreover, with accurate prognostic stratification and response assessment based on biomarkers of clonal and organ disease, we have learnt to safely apply treatments originally developed for multiple myeloma, to the fragile patients with AL amyloidosis.<sup>2,4,5</sup> Nevertheless, the timely recognition and the appropriate treatment of patients with AL amyloidosis remains challenging even for hematologists who are expert in multiple myeloma. In this review, we summarize the current knowledge on the pathogenesis of AL amyloidosis, and we focus on the clinical management of patients with this disease.

**The Amyloid Clone and Mechanisms of Organ Damage.** Not only is the amyloidogenic clone usually smaller in size than that causing multiple myeloma, but it is characterized by a significant frequency of chromosomal abnormalities, that can affect treatment outcomes. The most frequent is t(11;14) translocation, observed in almost 50% of patients.<sup>6</sup> The presence of t(11;14) is associated with poorer outcome with bortezomib-based and immunomodulatory (IMiDs)-based therapy, even when cyclophosphamide is added.<sup>7,8</sup> The adverse impact of t(11;14) can be overcome by melphalan, administered orally or in autologous stem cell transplant.<sup>9,10</sup> Gain of 1q21 is less frequent in AL amyloidosis than in multiple myeloma, being found in less than 20% of patients.<sup>6</sup> Patients harboring this abnormality have poorer outcome when treated with oral melphalan/dexamethasone (MDex) without the addition of bortezomib.<sup>11</sup> Clonal plasma cells in AL amyloidosis have similar phenotypic and copy number alteration profiles as those found in multiple myeloma, but their gene expression profile is similar to that of normal plasma cells.<sup>12</sup> A genome-wide association study showed a shared genetic susceptibility between AL amyloidosis and multiple myeloma, but cyclin D1 was a more prominent driver in AL amyloidosis.<sup>13</sup> The plasma cells rely on the proteasome to cope with the proteotoxicity exerted by the misfolded, amyloidogenic light chains.<sup>14-16</sup> This makes the amyloid plasma cell clone keenly sensitive to proteasome inhibitors.

The light chain variable region gene and the gene family of the clone can, at least in part, explain the variable organ tropism of AL amyloidosis. Indeed, three *Vλ* genes, *IGLV2-14*, *IGVL6-57*, and *IGLV3-1* contribute to encoding the majority of amyloidogenic  $\lambda$  light chains.<sup>17-19</sup> The germline gene *LV6-57* is common in AL amyloidosis while it is exceedingly rare in normal B-cells, and it is associated with renal involvement.<sup>20</sup> Usage of *LV1-44* germline gene is linked to predominant cardiac involvement, whereas *KV1-33* is associated with involvement of the liver.<sup>21</sup>

Since cardiac involvement is the main determinant of survival, efforts have been focused on unveiling the mechanisms of cardiac dysfunction in AL amyloidosis. The observation of complete clinical recovery of patients after effective chemotherapy in the absence of significant reduction of amyloid deposits indicates that the mass action caused by the deposits is not the only, and possibly not the main, determinant of organ dysfunction in AL amyloidosis. The availability of cardiac biomarkers, particularly N-terminal pro-natriuretic peptide type B (NT-proBNP) as a measure of amyloid cardiac dysfunction, showed that the clinical severity of heart failure and patient survival is linked to changes in the concentration of the circulating amyloidogenic free light chains rather than to changes in the amyloid load.<sup>22-24</sup> Indeed, the infusion of light chain purified from the urine of patients with cardiac amyloidosis causes a rapid increase in end-diastolic pressure in isolated mouse hearts in a matter of few minutes, which is not observed with control light chains.<sup>25</sup> Exposing *Caenorhabditis elegans*, a worm whose pharynx pulses rhythmically and is considered an analog of the vertebrate heart, to light chains of patients with cardiac AL amyloidosis, but not to control light chains, reduces the rate of pharynx contraction.<sup>26</sup>

Finally, the injection of light chains from patients with cardiac AL amyloidosis in the heart of zebrafish reduces the cardiac output and the lifespan of the fishes in the absence of amyloid deposits, which is not observed with control light chains.<sup>27</sup> Overall, this clinical and experimental evidence point to the toxicity exerted by the circulating precursor as the main cause of cardiac dysfunction in AL amyloidosis.<sup>28,29</sup>



**Figure 1. Organ involvement in 1065 patients with AL amyloidosis.** The patients were diagnosed between 2004 and 2015 at the Pavia Amyloidosis Research and Treatment Center. PNS, peripheral nervous system; ANS, autonomic nervous system.

**Clinical Presentation and Diagnosis.** The clinical manifestations of AL amyloidosis depend on organ involvement (**Figure 1**) but are rarely specific. Involvement of the soft tissues with macroglossia, periorbital purpura, submandibular gland swelling, and shoulder pad sign can easily trigger the diagnosis but are uncommon. More frequently, AL amyloidosis manifests with signs and symptoms resembling those of more common conditions of the elderly. Cardiac involvement (approximately 80% of patients) manifests with heart failure with preserved ejection fraction. Echocardiography is the cornerstone of the assessment of amyloid cardiomyopathy revealing increased ventricular wall thickness and granular sparkling. While ejection fraction is usually preserved until late stages of the disease, longitudinal strain, and midwall fractional shortening are often altered and have prognostic relevance.<sup>30,31</sup> Electrocardiogram usually shows low limb voltages in cardiac AL amyloidosis. Late gadolinium enhancement at cardiac magnetic resonance strongly points to the diagnosis of heart involvement; moreover, cardiac magnetic resonance can quantify the extracellular volume that may reflect the amyloid load.<sup>32</sup> The scintigraphy tracers developed for imaging the amyloid deposits in the brain of patients with Alzheimer disease, can identify cardiac amyloidosis and are promising tools for detecting and possibly quantitating amyloid deposits also in systemic amyloidoses.<sup>33</sup> The uptake of bone

tracers in patients with AL amyloidosis is absent or moderate, differently from transthyretin cardiac amyloidosis, characterized by a strong uptake. This difference can be used to distinguish between the two forms.<sup>34</sup> Increased concentrations of NT-proBNP are found in 100% of patients with cardiac AL amyloidosis, and precede symptoms and imaging alterations, allowing diagnosis at very early stages.<sup>22,35</sup> The kidney is involved in two-thirds of patients with AL amyloidosis. The disease manifests with albuminuria, evolving in nephrotic syndrome and progressing to renal failure eventually leading to end-stage renal disease if unrecognized or ineffectively treated. Involvement of the liver is characterized by organ enlargement without scan defects and elevation of alkaline phosphatase. Peripheral neuropathy is axonal, predominantly sensory and centripetal. Involvement of the autonomic nervous system is common but usually asymptomatic, although it can often become manifest with inappropriate use of hypotensive drugs. It is characterized by postural hypotension that can be preceded by the "resolution" of a pre-existing hypertension, erection defects in males and disturbances in bowel movements. General symptoms, most commonly profound fatigue and malnutrition, often accompany more organ-specific manifestations.

These clinical manifestations are not only resembling those of more common conditions, but they are usually associated with advanced stages

of the disease. All this, unfortunately, results in frequent diagnostic delays. A recent survey showed that 40% of patients with AL amyloidosis remain undiagnosed 1 year after the onset of symptoms.<sup>36</sup> Similar delays are also observed in patients who are performing regular follow-up for monoclonal gammopathy of undetermined significance (MGUS) under the supervision of hematologists.<sup>37</sup> This is because the classical workup of patients with MGUS does not include appropriate, sensitive tools for the detection of the onset of organ involvement. Thus, we advocated the inclusion of sensitive markers of cardiac (NT-proBNP) and renal (albuminuria) amyloidosis in the regular follow-up of patients with MGUS and abnormal free light chain (FLC) ratio.<sup>35,38</sup>

Once amyloidosis is suspected, the diagnosis requires the demonstration of amyloid deposits in a biopsy. The abdominal fat aspirate is simple and minimally invasive, although its interpretation requires expertise. In combination with biopsy of the bone marrow stained with Congo red and/or biopsy of a minor salivary gland, it can yield a diagnostic sensitivity of approximately 90%, thus sparing organ biopsies.<sup>39-41</sup> Nevertheless, organ biopsies may need to be performed in subjects with strong clinical suspicion and negative fat, gland, and bone marrow. Typing of the amyloid deposits is mandatory, in order to avoid misdiagnosis between AL amyloidosis and other common forms of systemic amyloidosis (listed in **Table 1**), such as hereditary or wild-type (formerly senile) transthyretin amyloidosis, hereditary apolipoprotein AI amyloidosis, leucocyte chemotactic factor-2 amyloidosis, and amyloidosis reactive to chronic inflammation. Incorrect typing could lead to disastrous therapeutic errors.<sup>42-44</sup> Unfortunately, light microscopy immunohistochemistry and immunofluorescence with commercial antibodies,

the most commonly available techniques, are unreliable to characterize amyloid deposits.<sup>45,46</sup> Thus, in most instances a reliable diagnosis requires referral of patients to specialized centers. Light microscopy immunohistochemistry can be reliably performed at referral centers using custom-made antibodies.<sup>47</sup> Immunoelectron microscopy with commercial antibodies can correctly identify the amyloid type in almost 100% of patients.<sup>40</sup> Mass spectrometry-based proteomics can be used on whole tissues or after laser capture microdissection to reliably type amyloid deposits.<sup>48,49</sup>

Once the diagnosis and typing of AL amyloidosis have been established, the diagnostic workup is completed by assessing the burden and severity of clonal and organ disease, as summarized in **Table 2**. Given the small size of the amyloid plasma cell clone, the combination immunofixation of both serum and urine with measurement of circulating free light chain is required to grant adequate sensitivity.<sup>50-53</sup> Assessment of organ involvement is based on biomarkers, electrocardiogram, and imaging studies.

**Staging.** The survival of patients with AL amyloidosis is exceedingly heterogeneous, depending on the severity of cardiac dysfunction at the time of diagnosis: while patients who are diagnosed late, at a stage when heart damage is very advanced and not amenable of improvement with treatment survive only a few weeks, patients without heart involvement can survive years even if they fail to respond to therapy. This extreme heterogeneity requires accurate prognostic stratification for establishing the best therapeutic approach, balancing treatment intensity and rapidity of action with patients' frailty, as well as for comparing results of clinical trials. The Mayo

**Table 1.** Common types of systemic amyloidosis.

Amyloid type	Precursor protein	Acquired / Hereditary	Organ involvement
Systemic AL	Monoclonal LCs	Acquired	All organs (except the brain)
Localized AL	Monoclonal LCs	Acquired	Skin, tracheobronchial tree, lungs, urinary bladder, (others)
ATTRwt	Wild type transthyretin	Acquired	Heart, soft tissue, lung
ATTRm	Mutated transthyretin	Hereditary	Hear, PNS/ANS
AA	Apolipoprotein serum amyloid A	Acquired	Kidney, heart, liver, lung
ApoAI	Apolipoprotein AI	Hereditary	Liver, testis, heart, PNS
ALECT2	Leukocyte Chemotactic Factor-2	Acquired	Kidney, primarily

The amyloid types are identified by acronyms where the letter "A" for amyloidosis is followed by the abbreviation of the protein forming the amyloid fibrils. ANS, autonomic nervous system; LCs, immunoglobulin light chains; PNS, peripheral nervous system.



**Table 2.** Assessment of clonal and organ disease in patients with AL amyloidosis.

<b>Assessment of clonal disease</b>	<ul style="list-style-type: none"> <li>• Serum <u>and</u> urine electrophoresis and immunofixation <u>and</u> serum free light chain measurement</li> <li>• Bone marrow aspirate / biopsy (plus FISH)</li> <li>• Imaging studies for bone disease</li> </ul>
<b>Assessment of organ disease</b>	<p><b>Heart</b></p> <ul style="list-style-type: none"> <li>• NT-proBNP (or BNP), cardiac troponins</li> <li>• Echocardiography (plus strain imaging)</li> <li>• ECG (plus Holter ECG)</li> <li>• Cardiac MRI (if indicated)</li> <li>• <sup>99m</sup>Tc-DPD or PYP scan (to rule out non-AL cardiac amyloidosis)</li> </ul> <p><b>Kidney</b></p> <ul style="list-style-type: none"> <li>• 24h urinary protein</li> <li>• Serum creatinine (and eGFR)</li> </ul> <p><b>Liver</b></p> <ul style="list-style-type: none"> <li>• Liver function tests</li> <li>• Liver US / CT scan (if indicated)</li> <li>• Liver elastography (if indicated)</li> </ul> <p><b>Nerves</b></p> <ul style="list-style-type: none"> <li>• Physical examination</li> <li>• Nerve conduction studies (if indicated)</li> <li>• Autonomic testing (if indicated)</li> </ul>

FISH, fluorescence in situ hybridization; NT-proBNP, N-terminal natriuretic peptide type B; Cardiac MRI, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate; US, ultrasound-sonography; CT, computer tomography.

Clinic group established a simple and reliable staging system based on NT-proBNP and cardiac troponins, which was then modified by European investigators (**Table 3**).<sup>54,55</sup> This staging system is now the most widely used for clinical trial design and patient management. Besides heart involvement, clonal burden, assessed by bone marrow plasma cell (BMPC) infiltration or dFLC (difference between involved and uninvolved circulating free light chains) has an independent impact on survival. Patients with AL amyloidosis and BMPC infiltrate >10% have a more reduced survival, which is comparable to that of patients who have concomitant overt multiple myeloma.<sup>56</sup>

Subjects who have a very low (<50 mg/L) dFLC level have a significantly better outcome across cardiac stages.<sup>57,58</sup> The Mayo Clinic group has incorporated the dFLC level in the cardiac staging system (**Table 3**).<sup>59</sup> The severity of renal involvement does not directly affect patient’s survival, but impacts the quality of life and reduces the access to effective therapy. A staging system predicting progression to dialysis has been proposed and validated by European investigators (**Table 3**).<sup>60</sup> Similarly to heart involvement, recognition and prompt treatment of renal AL amyloidosis at early stages can almost abolish the risk of progression to dialysis, while late diagnosis

**Table 3.** Staging of cardiac and renal damage in AL amyloidosis.

Staging system	Markers and thresholds	Stages	Outcomes*
Cardiac <sup>54,55</sup>	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI > 0.01 ng/mL)	I. no markers above the cutoff II. one marker above the cutoff IIIa. both markers above the cutoff and NT-proBNP <8500 ng/L IIIb. both markers above the cutoff and NT-proBNP ≥8500 ng/L	I. median survival not reached, 60% surviving 10 years II. median survival 49 months IIIa. median survival 14 months IIIb. median survival 5 months
Revised Mayo Clinic <sup>139</sup>	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I. 0 markers above the cutoff II. 1 marker above the cutoff III. 2 markers above the cutoff IV. 3 markers above the cutoff	I. median survival not reached, 55% surviving 10 years II. median survival 57 months III. median survival 18 months IV. median survival 6 months
Renal <sup>60</sup>	eGFR <50 mL/min per 1.73 m <sup>2</sup> proteinuria >5 g/24h	I. both eGFR above and proteinuria below the cutoffs II. either eGFR below or proteinuria above the cutoffs III. both eGFR below and proteinuria above the cutoffs	I. 1% risk of dialysis at 2 years II. 12% risk of dialysis at 2 years III. 48% risk of dialysis at 2 years

cTn, cardiac troponin; dFLC, difference between involved (amyloidogenic) and uninvolved circulating free light chain; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-natriuretic peptide type-B. \*Observed in 1065 patients with AL amyloidosis newly diagnosed at the Pavia Amyloidosis Research and treatment center.

at advanced stages is associated with higher risk of progression.

**Treatment.** The complexity of AL amyloidosis, which is due to the unique coexistence of a clonal plasma cell disorder and dysfunction multiple vital organs, makes treatment of this disease a challenge even for hematologists who are experts in the field of multiple myeloma. Indeed, the availability of new drugs, directly targeting the amyloid deposits, will probably displace AL amyloidosis from the realm of exclusive hematologic therapy. The experience of treating physicians significantly impacts patients' outcomes,<sup>61</sup> and very few recent prospective controlled studies exist to guide the therapeutic strategy. Thus, whenever possible, patients should be referred to specialized centers for treatment. Indeed, the amyloid clone requires treatment even if in the vast majority of cases it does not meet the criteria for treating multiple myeloma.<sup>62</sup> Moreover, differently from patients with multiple myeloma, subjects suffering from AL amyloidosis are at high risk of death and are extremely susceptible to treatment toxicity in the first few months after diagnosis; whereas, if they survive this first dangerous time, they enjoy a better long-term outcome compared to myeloma patients.<sup>63</sup> For this reason, chemotherapy is usually delivered at the lowest effective dose during the first cycles. The treatment strategy needs to be adapted to early treatment efficacy and should not be planned in advance. The response should frequently be assessed, at least every 2 cycles, in order to allow rapid switch to rescue therapy in patients who do not achieve satisfactory response. The criteria for hematologic,<sup>57,58,64</sup> cardiac,<sup>64</sup> and renal<sup>60</sup> response (summarized in **Table 4**) have been established and validated in a huge international effort and offer guidance to

individual patients treatment, as well as surrogate endpoints for clinical trials.<sup>65</sup> In particular, a new criterion where both hematologic and organ response can be assessed simultaneously early on in the treatment of AL amyloidosis was proposed to stratify the risk of patients, supporting its use as a surrogate end-point in clinical trials.<sup>66</sup> In addition, a recent report from Mayo Clinic showed that the better survival was assessed in patients who obtained the deeper organs (heart, kidney, liver).<sup>67</sup>

*Chemotherapy targeting the amyloid plasma cell clone.* Anti-plasma cell chemotherapy is the cornerstone of treatment of AL amyloidosis and was able to remarkably improve patients' outcomes over the last decades.<sup>5</sup> Treatment of AL amyloidosis should be adapted to the severity of organ involvement.

Low-risk patients represent approximately 15% of all subjects suffering from AL amyloidosis and can be considered for autologous stem cell transplantation (ASCT). This procedure is associated with a substantially higher risk of early mortality compared to multiple myeloma. However, refinement in selection criteria has reduced transplant-related mortality over time.<sup>61</sup> Accumulation of expertise is also crucial, the outcome being significantly poorer at centers where less than four transplants per year are performed in patients with this disease.<sup>61</sup> When an adequate selection of transplant candidates is applied at referral centers, the outcome is excellent, with hematologic response in 71% of subjects and complete response (CR) in 35-37%.<sup>61,68</sup> These results in overall median survival of 7.6 years.<sup>68</sup> The great majority of transplant-related mortality occur in patients with elevated cardiac biomarkers, and subjects whose NT-

**Table 4.** Validated criteria for response assessment in AL amyloidosis. Response criteria are validated in independent patient populations for use at 3 and 6 months after treatment initiation.

<b>Hematologic response</b>	<b>Definition</b>
Complete response (CR)	Negative serum and urine immunofixation and normal FLC ratio
Very good partial response (VGPR)	dFLC <40 mg/L
Partial response (PR)	dFLC decrease >50% compared to baseline
low-dFLC response*	dFLC <10 mg/L
<b>Cardiac response</b>	<b>Definition</b>
Pre-treatment NT-proBNP $\geq 650$ ng/L	Decrease of NT-proBNP by >30% and 300 ng/L
Pre-treatment NYHA class III or IV	At least 2 points decrease of NYHA class
<b>Renal response</b>	<b>Definition</b>
Pre-treatment proteinuria >0.5 g/24h	At least 30% decrease in proteinuria or drop below 0.5 g/24 hour, in the absence of renal progression defined as a >25% decrease in eGFR

\*in patients with baseline dFLC >20 mg/L and <50 mg/L.

FLC, free light chain; dFLC, difference between involved and uninvolved light chain; NT-proBNP, N-terminal pro natriuretic peptide type B; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate.

proBNP is >5000 ng/L and/or cTnT is >0.06 ng/mL should not be offered ASCT.<sup>69,70</sup> Other eligibility criteria are ejection fraction >45% at echocardiography, New York Heart Association (NYHA) class <III, orthostatic systolic blood pressure >90 mmHg, age <65 years, performance status (Eastern Cooperative Oncology Group) ≤2, eGFR >50 mL/min per 1.73 m<sup>2</sup> unless on dialysis, and lung CO diffusion capacity >50%.<sup>1,70,71</sup> Patients who do not obtain CR after ASCT can receive bortezomib-based treatment. Overall, this sequential approach yields a 60% rate of CR.<sup>72</sup> Induction therapy with bortezomib before ASCT improves outcomes in patients with a bone marrow plasma cell infiltrate >10%.<sup>73</sup>

Intermediate risk patients account for approximately 70% of patients with AL amyloidosis. They receive non-transplant chemotherapy. Until recently, a standard treatment for these patients has been oral melphalan and dexamethasone (MDex).<sup>74,75</sup> This regimen is very well tolerated and yields a 76% overall hematologic response rate, with CR in 31% of cases.<sup>76</sup> A randomized trial compared MDex to ASCT and failed to demonstrate an advantage for ASCT in terms of response rate and survival.<sup>77</sup> This trial was performed before the availability of a biomarker-based selection of transplant candidates, and the results were considered influenced by very high transplant-related mortality. Nevertheless, a landmark analysis excluding early deaths confirmed these results. Bortezomib-based regimens are now considered upfront standards of care in most patients with AL amyloidosis. A large retrospective study and a prospective trial showed efficacy of bortezomib in relapsed / refractory patients.<sup>78-81</sup> In the largest study of frontline treatment with cyclophosphamide, bortezomib and dexamethasone (CyBorD), the overall hematologic response rate was 60%, with CR in 23% of cases.<sup>82</sup> Two retrospective case-control studies showed higher response rates with bortezomib in combination with alkylating agents and dexamethasone compared to the previous standards of care MDex and cyclophosphamide / thalidomide / dexamethasone, though without a survival benefit.<sup>83,84</sup> An international phase III study (NCT01277016) comparing MDex with bortezomib plus MDex (BMDex) has recently been completed, showing significantly higher overall hematologic response rate with BMDex

(81% vs. 57%, P=0.005).<sup>85</sup> Based on this data, bortezomib should be offered to intermediate-risk patients, in the absence of contraindications such as peripheral neuropathy. The choice of the best combination should take into account clonal and patient characteristics. A recent study by Kastritis, et al. showed that addition of cyclophosphamide and higher doses of dexamethasone do not improve outcomes of patients with AL amyloidosis treated with bortezomib.<sup>86</sup> Treatment with BMDex has the advantage of overcoming the effects of both gain 1q21 (poor outcome with oral melphalan) and t(11;14) (poor outcome with bortezomib).<sup>7,8,10,11</sup> Oral melphalan should not reach the cumulative dose of 150 mg (not exceeding 2 cycles) in patients who may be selected for subsequent stem cell mobilization and harvest.<sup>87</sup> Treatment with bortezomib / dexamethasone alone or in combination with cyclophosphamide is preferred in patients with potentially reversible contraindication to ASCT, being stem cell sparing, as well as in subjects with renal failure.

The remaining 15-20% of patients with AL amyloidosis are high-risk, most frequently because of advanced cardiac stage (IIIb) or severe heart failure (NYHA class III or IV). So far, no treatment approach, including those based on bortezomib, was able to overcome the poor prognosis of these patients, and median survival ranges from 3 to 7 months.<sup>88</sup> Nevertheless, the few patients who survive long enough (at least 3 months) to take advantage of response to chemotherapy enjoy prolonged survival.<sup>82</sup> A recent report from The United Kingdom Group showed that patients achieving a rapid response at day 30 or overall CR/VGPR at 6 months had markedly better survival.<sup>89</sup> High-risk patients are treated with low-dose combinations, with weekly dose escalation based on tolerability under intensive monitoring.<sup>1</sup>

Relapsed patients have a good prognosis, with remarkably longer survival than refractory subjects.<sup>90</sup> There is no consensus on criteria to start rescue therapy in relapsing subjects.<sup>91</sup> Cardiac progression should not be awaited, because it is associated with shorter survival.<sup>90</sup> Relapsing patients can be treated by repeating upfront therapy, if possible, although this is associated with shorter time to retreatment without reduction in overall survival.<sup>92</sup> When this is not possible, relapsed patients should be treated as

subjects failing to respond to upfront therapy. A recent report defined that a potential role of deferred ASCT in both a consolidation or relapse setting in selected patients with cardiac AL who have achieved organ responses.<sup>93</sup> Immunomodulatory drugs (IMiDs) are the backbone of second-line therapy. Lenalidomide is able to overcome resistance to alkylating agents, proteasome inhibitors, and thalidomide.<sup>94-99</sup> However, this drug can cause worsening renal failure in patients with renal AL amyloidosis with significant proteinuria.<sup>100</sup> Lenalidomide combinations have been used also upfront with encouraging results.<sup>97,98,101-104</sup> Pomalidomide is one of the most powerful agents in refractory AL amyloidosis, being able to rescue patients refractory to alkylators, first- and second-generation proteasome inhibitors, and lenalidomide.<sup>105-107</sup> Hematologic response to pomalidomide is obtained rapidly, in a median time of 1 month, and is observed in more than 60% of patients.<sup>107</sup> Complete responses are relatively rare with IMiDs in pre-treated patients. However, the use of IMiDs could result in long progression-free intervals and survival rates among patients with AL amyloidosis.<sup>108</sup> Newer agents have been tested in the relapsed / refractory setting. The proteasome inhibitor carfilzomib yielded a hematologic response rate of 63% (CR 12%).<sup>109</sup> In this study, 39% of patients had NT-proBNP progression, which was clinically relevant in 18% of cases. The cardiac toxicity of carfilzomib is a cause of concern in AL amyloidosis. The oral proteasome inhibitor ixazomib proved active in pre-treated patients, particularly in those who were not previously exposed to bortezomib, and is currently being tested in a randomized phase III trial in relapsed / refractory patients (NCT01659658).<sup>110</sup> Thus, ixazomib seems particularly suitable for upfront combinations, allowing oral proteasome inhibitor-based regimens. Indeed, 2 trials of ixazomib, cyclophosphamide and dexamethasone (NCT03236792, NCT01864018) are ongoing in the upfront setting. Daratumumab is one of the most promising new agents for the treatment of patients with AL amyloidosis. A recently published series of previously treated subjects who received daratumumab reported a rapid (median 1 month) hematologic response in 76% of patients with 36% CRs.<sup>111</sup> In the 2017 American Society of Hematology meeting, two different abstracts reported the preliminary data of prospective

ongoing clinical trials about the use of daratumumab in relapse/refractory setting.<sup>112,113</sup> Daratumumab will likely be moved to upfront therapy in combination with proteasome inhibitor-based regimens in the near future. Indeed, a phase III randomized trial of daratumumab in combination with CyBorD vs. CyBorD alone in newly-diagnosed patients will be opened shortly (NCT03201965).

*Interfering with amyloidogenesis and organ damage and targeting the amyloid deposits.* New, non-hematologic, approaches specifically targeting steps that are downstream in the pathogenic cascade are emerging as supplements of anti-plasma cell therapy, given in combination with chemotherapy or after achievement of hematologic response. Following the observation of the efficacy of the anthracycline 4'-iodo-4'-deoxydoxorubicin on amyloidogenesis in vitro and reports of clinical improvements in subjects with AL amyloidosis, related non-cytotoxic and non-cardiotoxic compounds were investigated.<sup>114-118</sup> Amongst them, doxycycline was able to disrupt amyloid fibrils in transgenic mouse models of systemic amyloidosis,<sup>119,120</sup> and protected the *C. elegans* model from the effects of cardiotoxic amyloid light chains.<sup>26</sup> In a retrospective case-control study the administration of doxycycline as antibiotic prophylaxis during chemotherapy for AL amyloidosis reduced early mortality, resulting in higher response rates and survival improvement.<sup>121</sup> A phase III trial of chemotherapy with or without doxycycline is being designed. Polyphenols can redirect amyloidogenic polypeptides into unstructured, off-pathway oligomers.<sup>122</sup> Amongst them epigallocatechin-3-gallate was tested (EGCG) showed promising activity on cardiac AL amyloidosis in case reports and retrospective series.<sup>123-125</sup> In a phase II trial, EGCG was well tolerated and in some patients a decrease in albuminuria was observed.<sup>126</sup>

The amyloid deposits are natural targets of novel therapies. United Kingdom investigators designed a compound CPHPC that avidly binds to serum amyloid P component (SAP) a protein that coats the amyloid fibrils protecting them from degradation. This compound is used to remove SAP from the bloodstream<sup>127</sup> before the administration of an anti-SAP antibody that promotes a complement-dependent, macrophage-derived reaction that removes visceral amyloid



deposits.<sup>128</sup> This combination approach was tested in a pilot clinical study,<sup>129</sup> and a trial in patients with cardiac AL amyloidosis is ongoing (NCT03044353). The report of the ability of this approach to induce organ response measured with validated criteria is eagerly awaited. Antibodies directly targeting the amyloid deposits have also been developed. One of them, 11-1F4, has been tested in phase I clinical trial, showing promising organ response in an interim analysis.<sup>130</sup> Those data were recently updated at the last ASH meeting.<sup>131</sup> A different antibody, NEOD001 is currently in the most advanced stage of clinical development. In a phase I/II study in patients with AL amyloidosis who had completed chemotherapy, cardiac and renal response rates were 57% and 60%, respectively.<sup>132</sup> Organ response to NEOD001 was independent of rate and depth of previous hematologic response.<sup>133</sup> Two phase III randomized, placebo-controlled trials of NEOD001 combined with bortezomib-based chemotherapy in newly-diagnosed patients (NCT02312206), and as single agent in subjects who completed chemotherapy (NCT02632786) have recently completed enrollment and results are eagerly awaited.

*Supportive therapy.* Supportive treatment is vital in patients with AL amyloidosis, in order to sustain organ function while chemotherapy takes effect, and to improve quality of life. However, treatment of concomitant heart failure and nephrotic syndrome in patients who often have concomitant involvement of the autonomic nervous system is extremely complicated, and should be done under close supervisions of specialized cardiologists and nephrologists who have experience in the treatment of patients with systemic amyloidosis. In some patients, asymptomatic involvement of the autonomic nervous system<sup>134</sup> could lead to overt, often severe hypotension when treatment with angiotensin-converting enzyme inhibitors is established. This therapy should be considered with caution and at the lowest effective dose. The development of a significant peripheral edema requires diuretics associated with dietary sodium restriction. Patients weigh themselves daily, and diuretic dosing should be titrated accordingly. It should be kept in mind that in patients with heart involvement cardiac function is preload dependent and

reduction of intravascular volume should be avoided. Patients with recurrent arrhythmic syncope may benefit from pacemaker implantation; whereas, the use of implantable ICD is controversial. Gabapentin or pregabalin can be used to control neuropathic pain and octreotide can control diarrhea. Nutritional status is also frequently compromised in AL amyloidosis, independently affecting quality of life assessment.<sup>135-137</sup> Nutritional counseling is effective in improving mental quality of life and is associated with better survival.<sup>138</sup> Cardiac and renal transplant can be considered in patients who attain CR but are dialysis dependent or have persistent, severe heart failure. Moreover, young patients with isolated, advanced cardiac involvement may be considered for heart transplant followed by effective chemotherapy aiming at rapidly achieving CR.

**Conclusions.** Despite the recent advances the management of AL amyloidosis remains highly challenging and characterized by still unmet needs. The appropriate management of AL amyloidosis requires 1) early diagnosis, 2) correct typing, 3) accurate risk stratification and effective therapy guided by frequent careful assessment of response. Early diagnosis lies in the hands of general hematologists who are responsible for the follow-up of patients with MGUS. The onset of cardiac and renal involvement by AL amyloidosis in these subjects can be detected at a pre-symptomatic stage with simple markers, albuminuria and NT-proBNP, that should be part of the follow-up panel of patients with MGUS and abnormal FLC ratio. Amyloid typing is mandatory but requires advanced technology that needs to be concentrated at referral centers. The lack of controlled prospective studies and the importance of a critical level of expertise in specific and supportive therapy, also requires referral of patients to specialized centers whenever possible. Coordinated national networks are vital in sharing knowledge at rendering it accessible to patients. In the near future, the availability of newer powerful anti-plasma cell drugs, combined with anti-amyloid agent will hopefully further improve the outcome of patients with AL amyloidosis. Still clinical practice and research cannot be disconnected in this complex and dreadful disease.

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