Individualized Approach to Management of Light Chain Amyloidosis

Giovanni Palladini, MD, PhD,1,2 and Paolo Milani, MD, PhD1,2

ABSTRACT

Systemic light chain (AL) amyloidosis is caused by a B-cell (most commonly plasma cell) clone that produces a toxic light chain that forms amyloid fibrils in tissues and causes severe, progressive organ dysfunction. The clinical presentation is protean, and patients are usually extremely frail, thus requiring careful adaptation of the treatment approach. However, the severity of organ involvement can be accurately assessed with biomarkers that allow a sharp prognostic stratification and precise tailoring of the treatment strategy. Moreover, the availability of biomarker-based response criteria also allows adjustment of the treatment approach over time. The recent completion of 3 large randomized clinical trials has offered new evidence for designing appropriate treatments. All this information has recently been integrated in the joint guidelines of the International Society of Amyloidosis and the European Hematology Association for the treatment of AL amyloidosis. Other clinical trials are underway testing new agents directed against the amyloid clone and the amyloid deposits. Our understanding of the peculiarities of the amyloid clone, as well as our ability to detect residual clonal disease and improve organ dysfunction, are also being refined and will result in more precise personalization of the treatment approach.

Systemic light chain (AL) amyloidosis is caused by a B-cell clone that produces a monoclonal light chain that aggregates and deposits in target organs forming amyloid deposits.1 The amyloid clone is most commonly composed of plasma cells and is small in size, with a median infiltrate of approximately 10%; however, in approximately 5% of patients, it is formed of lymphoplasmacytic cells or other B cells. The clinical presentation is determined by the pattern of organ involvement, and cardiac amyloidosis is associated with the worst outcome. Patients in whom the heart is not involved can survive long times even if they do not experience response to up-front therapy, whereas subjects with advanced heart involvement at diagnosis have a very poor survival and often die before treatment has a chance to take effect. However, even at advanced stages, rapid response to therapy can restore organ dysfunction and prolong survival.2–5 Yet, the extreme frailty of these patients makes it often difficult to deliver effective treatment in time. This highlights the need for a rapid and correct diagnosis, based on a biopsy-proven approach. Correct amyloid typing according to the recently published indication of the International Society of Amyloidosis, performed using accepted techniques, is also mandatory for all cases.6 Currently, treatment of AL amyloidosis is based on chemotherapy/immunotherapy targeting the amyloid clone, whereas approaches targeting the amyloid deposits are being tested in clinical trials.7,8 Physicians treating patients with AL amyloidosis have always had the perception that treatment needed to be tailored to patients’ frailty,9 and the peculiarities of this disease, in which a small, indolent hematologic malignancy produces a toxic protein that causes devastating organ dysfunction, stimulated the development and validation of tools to assess patients’ frailty and to monitor treatment efficacy. The possibility of measuring the amyloid precursor with free light chain (FLC) assays and the availability of robust markers of organ involvement generated a wealth of knowledge that was incorporated in the design of the most recent and relevant controlled trials, and guided the application of their results in clinical practice.10 Now, the ever-improving knowledge of the characteristics of the amyloid clone and mechanisms of organ damage, and the availability of powerful effective therapies are moving the management of AL amyloidosis to
the realm of personalized medicine. This review discusses how available knowledge allows the management of patients with AL amyloidosis to be individualized, from the selection of up-front therapy to the detection and management of refractory and relapsed disease.

**Selection of Up-Front Therapy**

The clinical presentation and outcome of patients with AL amyloidosis is highly heterogeneous. Patients can be classified according to the severity of cardiac and renal involvement with staging systems based on biomarkers of organ dysfunction and damage and on the level of differential FLC (dFLC). Staging is fundamental in the initial approach to patients, but it is not the only parameter to be considered in the selection of the up-front treatment strategy. The International Society of Amyloidosis (ISA) and European Hematology Association (EHA) recently issued guidelines for the treatment of AL amyloidosis (Figure 1). These guidelines are a first attempt to tailor treatment based on disease stage, age, and comorbidities, in light of the results of recent randomized trials. The first step is assessing eligibility to autologous stem cell transplant (ASCT). Transplant is highly effective but requires an extremely careful patient selection to avoid unacceptable early mortality. With refined eligibility criteria, transplant-related mortality drops to approximately 3% and hematologic response can be attained in 84% of patients, with very good partial response (VGPR) in 33% of cases and complete response (CR) in 39%. In eligible patients (Figure 1), pretransplant induction with daratumumab/cyclophosphamide/bortezomib/dexamethasone (Dara-CyBorD) or CyBorD alone is generally advised and specifically recommended in patients whose bone marrow plasma cell infiltrate is >10%. If CR is reached after induction alone, ASCT can be deferred. At our center, we apply a response-driven sequential treatment approach to patients eligible for ASCT, proceeding to transplant only in those who do not attain CR or VGPR plus organ response after induction. With this strategy, treatment-related mortality was lower than 1%, and 76% of patients obtained hematologic response (CR, 34%; VGPR, 29%). In patients who attain less than a satisfactory response to induction and in those with concomitant multiple myeloma, ASCT is performed with intravenous melphalan at 200 mg/m². Lower melphalan doses can be considered at referral centers in subjects with renal failure. Patients who attain at least VGPR after ASCT can be monitored without further treatment. Maintenance is not generally recommended, but can be considered (dose-adjusted lenalidomide) in patients with concomitant multiple myeloma.

Patients who are not eligible for ASCT should first be assessed for potential contraindication to bortezomib. The most common contraindication is peripheral neuroathy, which is present in approximately 15% of patients, but pulmonary fibrosis should also be considered. In the absence of contraindications to bortezomib, the treatment choice should be based on cardiac staging according to the European modification of the Mayo 2004 staging system. In patients with stage I, II, and IIIa AL amyloidosis, the first option should be Dara-CyBorD. This regimen was compared with CyBorD in the randomized phase III ANDROMEDA trial, and proved superior in terms of overall best hematologic response (92% vs 77%), rate of VGPR or better (79% vs 49%), and CR by ISA criteria (54% vs 27%), as well as cardiac (42% vs 22%) and renal (53% vs 24%) response at 6 months. Based on these favorable results, Dara-CyBorD was labeled for the treatment of AL amyloidosis by regulatory agencies in Europe and the United States. When daratumumab is not accessible, patients can be treated with bortezomib/melphalan/dexamethasone (BMDex). In a phase III clinical trial, BMDex had higher rates of overall hematologic response (81% vs 57%) and VGPR (41% vs 19%) than MDex alone, whereas CR rate was not significantly different (23% vs 20%). Importantly, for now, this is the only study proving an overall survival advantage for patients treated in the experimental arm. Yet, melphalan can jeopardize a subsequent stem cell collection. Thus, if daratumumab is not available, CyBorD can be preferred over BMDex in patients with potentially reversible contraindications to ASCT. Indeed, response to up-front bortezomib-based therapy can render patients who were excluded from ASCT eligibility, and in Europe ASCT is more frequently used in subsequent lines of therapy than up front. In patients with stage IIIb AL amyloidosis, defined as having elevated cardiac troponin (I >100 ng/L or T >35 ng/L or high-sensitivity troponin T >45 ng/L) and a concentration of N-terminal pro-type-B natriuretic peptide (NT-proBNP) >8,500 ng/L (or BNP >700 ng/L), the ISA/EHA guidelines suggest using the same regimens used in patients with less advanced disease but reducing the dose of dexamethasone (maximum 20 mg) and bortezomib (escalating from 0.7 mg/m²). Daratumumab does not require dose adjustments in this setting and can also be used as a single agent. A phase II study indicated that single-agent daratumumab was associated with a favorable safety profile and induced deep and rapid hematologic responses in patients with stage IIIb disease. If bortezomib is contraindicated, the ISA/EHA guidelines recommend single-agent daratumumab as a first option, as well as lenalidomide. The latter can be combined with dexamethasone and cyclophosphamide or melphalan. These regimens grant a hematologic response in 50% to 60% of cases, but deep responses tend to be rarer than with other agents. Possible alternatives are oral MDex, carfilzomib, and dexamethasone in patients without relevant cardiac involvement, and venetoclax in patients whose plasma cell clone harbors the t(11;14) abnormality. However, venetoclax has not yet been studied in the up-front
**Assess Eligibility for ASCT**

<table>
<thead>
<tr>
<th>Clinical Evaluation</th>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Age</td>
<td>≤65 y</td>
<td>-</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0-2</td>
<td>-</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Supine systolic blood pressure ≥90 mm Hg</td>
<td>Refractory orthostatic hypotension</td>
</tr>
<tr>
<td>Heart</td>
<td>• NYHA class I or II • EF ≥40% • Cardiac stage I or II • NT-proBNP &lt; 5,000 ng/L • cTnT &lt; 60 ng/L</td>
<td>• Symptomatic and/or refractory arrhythmias • Uncompensated heart failure</td>
</tr>
<tr>
<td>Liver</td>
<td>Direct bilirubin &lt; 2 mg/dL</td>
<td>-</td>
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<tr>
<td>Kidney</td>
<td>eGFR &gt; 50 mL/min</td>
<td>-</td>
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<tr>
<td>Respiratory function</td>
<td>sO2 ≥95% on room air DLco &gt; 50%</td>
<td>Symptomatic and/or refractory pleural effusions</td>
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<tr>
<td>Hemorrhagic risk</td>
<td>-</td>
<td>• Factor X &lt; 25% • GI involvement with active bleeding or risk of bleeding</td>
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</table>

**Induction**
- Dara-CyBorD or CyBorD

**Response assessment**
- CR
- <CR

**Follow-up**
- Rescue

**ASCT**

**Assess contraindication to bortezomib**

**Bortezomib-based therapy possible**

**Contraindication to bortezomib**

**Stage I−IIa**
- Dara-CyBorD
- BM Dex
- CyBorD

**Stage IIIb attenuated**
- Dara-CyBorD
- BM Dex
- CyBorD

**Single-agent daratumumab**
- CLD
- LM Dex
- Carfilzomib
- Venetoclax

**Response assessment**
- ≥VGPR
- <VGPR

**Follow-up**
- Rescue

**Individualized Management of AL REVIEW**

**Abbreviations:** AL, systemic light chain; ASCT, autologous stem cell transplant; BM Dex, bortezomib/melphalan/dexamethasone; CLD, cyclophosphamide/lenalidomide/dexamethasone; CR, complete response; cTnT, cardiac troponin T; CyBorD, cyclophosphamide/bortezomib/dexamethasone; Dara, daratumumab; DLco, diffusing capacity of the lung for carbon monoxide; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; LM Dex, lenalidomide/melphalan/dexamethasone; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PS, performance status; sO2, oxygen saturation; VGPR, very good partial hematologic response.

**Figure 1.** Treatment algorithm for patients with newly diagnosed AL amyloidosis.
setting. Carfilzomib should be considered for patients with renal involvement, and with great caution in those with nonsevere cardiac damage. Therefore, it can play a role in patients with isolated neuropathic involvement.17,33

For now, treatment tailoring has been mainly based on disease stage and comorbidities. However, clonal characteristics also affect treatment selection, and our increasing understanding of the amyloid clone will likely expand their role. Approximately 5% of patients with systemic AL amyloidosis harbor an IgM-producing clone. These clones can be formed of plasma cells, but they often have a lymphoplasmacytic phenotype. According to the ISA/EHA guidelines, the treatment of choice in these patients is rituximab + bendamustine.17 The overall hematologic response rate to this combination is 60% (CR, 14%; VGPR, 32%).34 The most common chromosomal abnormality in plasma cell amyloid clones is t(11;14), which is found in approximately 50% of patients. This is associated with lower response rates and poorer survival in patients treated with CyBorD, but not with oral or intravenous melphalan.35,36 However, the presence of t(11;14) did not reduce the efficacy of Dara-CyBorD,23 and if daratumumab is accessible, this chromosomal abnormality should not affect the choice of treatment. When daratumumab is not accessible, patients whose amyloid clones harbor t(11;14) should be treated with melphalan—either high-dose if they are eligible for ASCT or in the BM Dex combination. Venetoclax is also an appealing option for these patients, and studies in the up-front setting are awaited. The second most common chromosomal abnormality is amp(1q21), which is observed in approximately 20% of patients. This abnormality is associated with lower response rates and shorter survival with oral melphalan, and with poorer hematologic event-free survival with lenalidomide.37,38 The Heidelberg and Boston University groups independently reported that amp(1q21) had a detrimental effect on response rates and survival in patients treated with daratumumab, mostly in the relapsed/refractory setting.39–41 In the ANDROMEDA study, rate and depth of hematologic response to Dara-CyBorD were unaffected by the presence of amp(1q21).23

**Monitoring Response to Treatment**

In systemic AL amyloidosis, monitoring during and after therapy should be extremely close to identify patients whose disease is refractory to treatment and whose depth of hematologic response is not sufficient to grant recovery of organ dysfunction as early as possible. Our approach to individualize treatment and follow-up of patients with AL amyloidosis based on depth of hematologic and organ response is reported in Figure 2. Assessment of treatment efficacy should be based on validated criteria that predict survival outcome (Table 1).14,42–43 Early and deep reductions of amyloid FLC are crucial to save lives also in patients with advanced disease.2–4 Patients who do not rapidly attain VGPR should be shifted to rescue therapy. A recently published analysis from the London group suggested that a dFLC >400 mg/L and no response at 1 month after therapy were significant predictors of no improvement in response among patients treated mainly with a bortezomib-based approach.44 Prospective data are needed to evaluate the prognostic role of a so close evaluation of response in patients treated with a daratumumab-based approach. At the end of up-front therapy, a satisfactory response should be reached. Unfortunately, we still lack a definition of what an optimal response should be at this stage. However, it seems reasonable to aim for hematologic CR, or possibly less profound hematologic response if this is associated with
organ response, indicating that the residual amount of amyloid FLC is not enough to prevent organ recovery. Organ response can be reached as early as 3 months after treatment initiation. Early cardiac response is also possible in patients with advanced, stage IIIb heart involvement and is associated with improved overall survival. However, organ response can frequently lag behind hematologic response, and in the absence of early organ improvement, one should not too hastily conclude treatment failure. Nevertheless, organ response should be reached within 1 year and should progressively improve. A large international effort led by Mayo Clinic investigators is validating graded criteria for cardiac, kidney, and liver response that will be useful in long-term monitoring. Adequate suppression of amyloid FLC production should eventually translate in recovery of organ dysfunction. Nevertheless, approximately 30% to 40% of patients who attain hematologic CR fail to reach organ response. This might be due to irreversible organ damage. Yet, several studies suggested that persisting minimal residual disease (MRD), likely producing extremely low, undetectable amounts of amyloid FLC, can be responsible for persisting organ damage in these patients. If this is confirmed in larger studies, patients with sustained hematologic CR who do not achieve organ response might be tested for MRD, and start a further line of anticlonal therapy in case it is detected.

A major unmet need in the management of AL amyloidosis is a validated definition of hematologic progression. Cardiac and renal progression criteria have been validated and predict a poorer overall survival. However, precisely for this reason, identification of a cardiac or renal progression should not be considered the only trigger to start a rescue regimen. Ideally, hematologic progression criteria would be needed that anticipate organ progression. Current consensus criteria for hematologic progression are not validated and require a relatively high increase in FLC. Thus, in most instances, treatment is initiated before these criteria are met, and there is no agreement on what should trigger rescue therapy. The lack of validated criteria for hematologic progression not only impacts on the management of individual patients but also reduces the clinical relevance of definitions of progression-free survival currently used in clinical trials.

### Rescue Therapy
Therapy for patients who have relapsed/refractory AL amyloidosis is individualized based on previous exposure to anti-plasma cell agents. Patients in need of rescue chemotherapy because of unsatisfactory response to previous treatment lines or due to refractory disease can be considered for ASCT if they are eligible. This can also be considered in patients who were transplanted up front. In particular, a second ASCT can restore response in patients experiencing relapse who attained a durable hematologic response after ASCT. Yet, advances in nontransplant chemotherapy restrict second ASCT to highly selected patients.

Patients who did not receive proteasome inhibitors (PI) up-front or who had sustained hematologic response to a PI-containing regimen can be offered combinations including PI. Bortezomib can be combined with daratumumab in the relapsed/refractory setting. This combination was tested in a retrospective series in daratumumab-naïve patients and proved highly effective. The largest study to date reported a hematologic response rate of 66% (CR, 11%; VGPR, 55%). The bortezomib/dexamethasone combination used up front (BMDex, CyBorD) can also be used in patients with relapsed/refractory disease, although these combinations have not been extensively studied in this setting. However, bortezomib/dexamethasone alone is known to be effective as a rescue treatment (hematologic response, 68%; CR, 20%). The second-generation oral PI ixazomib in combination with dexamethasone was compared with physicians’ best choice (most

### Table 1. Hematologic and Organ Response Criteria According to the International Society of Amyloidosis

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Definition</th>
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<tr>
<td><strong>ISA Hematologic Response Criteria</strong></td>
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<tr>
<td>Complete response</td>
<td>Negative serum and urine immunofixation plus normal FLC ratio (normal FLC ratio not needed if iFLC &lt; uFLC)</td>
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<tr>
<td>Very good partial response</td>
<td>dFLC level &lt;40 mg/L</td>
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<tr>
<td>Partial response</td>
<td>dFLC decrease &gt;50% compared with baseline</td>
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<tr>
<td><strong>ISA Organ Response</strong></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>NT-proBNP (or BNP) decrease &gt;30% compared with baseline that must also be &gt;300 ng/L (or &gt;50 ng/L for BNP)</td>
</tr>
<tr>
<td>Kidney</td>
<td>24-hour proteinuria decrease &gt;30% compared with baseline in the absence of worsening (&gt;25% decrease) eGFR</td>
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Abbreviations: BNP, B natriuretic peptide; dFLC, difference between involved and uninvolved free light chain; eGFR, estimated glomerular filtration rate; FLC, free light chain; ISA, International Society of Amyloidosis; iFLC, involved free light chain; uFLC, uninvolved free light chain; NT-proBNP, N-terminal pro-type B natriuretic peptide.
commonly lenalidomide-based) in a recently published phase III study.\textsuperscript{39} Hematologic response was not significantly higher with ixazomib (63%; CR, 33%; VGPR, 15%) than in the comparator arm; however, patients in the experimental arm enjoyed longer time to vital organ deterioration and mortality, progression-free survival, and time to subsequent therapy than those receiving physician’s choice.\textsuperscript{59}

Patients who are refractory to up-front bortezomib and are daratumumab-naïve can receive daratumumab either as a single-agent or combined with lenalidomide.\textsuperscript{17} Daratumumab monotherapy was studied in a large retrospective series that reported a hematologic response rate of 64% (CR, 8%; VGPR, 48%).\textsuperscript{39} This approach was evaluated in 2 independent phase II clinical trials that produced discordant results in terms of treatment response: 90% (CR, 41%; VGPR, 45%) and 55% (CR, 8%; VGPR, 40%) in the Boston University and European studies, respectively.\textsuperscript{60,61} Daratumumab can also be combined with lenalidomide. In a large retrospective study, the Heidelberg group showed that this combination was very effective (hematologic response, 84%; CR, 16%; VGPR, 65%).\textsuperscript{40} In patients already exposed to daratumumab, lenalidomide/dexamethasone can be used alone. This combination was reported to induce a hematologic response in 31% of patients (CR, 5%; VGPR, 15%) in a recent large retrospective study.\textsuperscript{38}

Patients who are refractory to lenalidomide can be treated with pomalidomide. A large European retrospective study showed that this agent induced a hematologic response of 44% (CR, 3%; VGPR, 23%) in heavily pre-treated subjects who were mostly refractory to bortezomib, lenalidomide, and PIs.\textsuperscript{62} A new possible strategy under investigation is belantamab mafodotin, a monoclonal antibody targeting the B-cell maturation antigen conjugated to a microtubule-disrupting agent, monomethyl auristatin F. A prospective trial is underway (ClinicalTrials.gov identifier: NCT04617925) and 2 recently published retrospective series reported promising response data.\textsuperscript{63,64}

A very promising agent in patients whose clone harbors the t(11;14) is venetoclax. Prospective studies are awaited, but a retrospective series showed that in these subjects the hematologic response rate can be exceptionally high (81%) and profound (CR, 41%; VGPR, 37%).\textsuperscript{65}

Finally, the addition of doxycycline to chemotherapy was tested as a possible way to increase organ recovery based on different preclinical studies\textsuperscript{66} and 2 retrospective series.\textsuperscript{67,68} However, a recently published study failed to demonstrate the improvement in terms of progression-free survival among patients treated with CyBorD + doxycycline and those who did not receive this drug.\textsuperscript{69} Therefore, the European study on use of this antibiotic approach was terminated early due to slow enrollment rate.

**Conclusions**

Despite the rarity of the disease, AL amyloidosis has always had a calling to individualized medicine due to the extreme heterogeneity of clinical presentation and the availability of validated staging systems and response criteria based on biomarkers. The choice of treatment is currently based on staging and assessment of comorbidities, but better understanding of the amyloid clone and availability of novel targeted therapy will further refine personalization of treatment approaches. Moreover, there is the hope that immunotherapy directed against the amyloid deposits could be coupled with anti–plasma cell treatment. Currently 2 antiamyloid monoclonal antibodies (birtamimab and CAEI-101)\textsuperscript{70,71} are being tested in combination with anti–plasma cell chemotherapy/immunotherapy in 3 randomized clinical trials in patients with cardiac involvement. These agents have the potential to improve outcomes of patients with advanced disease and, together with the new powerful agents targeting the clone, are expected to be integrated into the more advanced patient-tailored treatment approach.

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