THERAPY IN PRACTICE

Diagnosis and Treatment of AL Amyloidosis

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Abstract

Systemic light chain (AL) amyloidosis is caused by an usually small B cell clone that produces a toxic light chain forming amyloid deposits in tissue. The heart and kidney are the major organs affected, but all others, with the exception of the CNS, can be involved. The disease is rapidly progressive, and it is still diagnosed late. Screening programs in patients followed by hematologists for plasma cell dyscrasias should be considered. The diagnosis requires demonstration in a tissue biopsy of amyloid deposits formed by immunoglobulin light chains. The workup of patients with AL amyloidosis requires adequate technology and expertise, and patients should be referred to specialized centers whenever possible. Stagings are based on cardiac and renal biomarkers and guides the choice of treatment. The combination of daratumumab, cyclophosphamide, bortezomib and dexamethasone (dara-CyBorD) is the current standard of care. Autologous stem cell transplant is performed in eligible patients, especially those who do not attain a satisfactory response to dara-CyBorD. Passive immunotherapy targeting the amyloid deposits combined with chemo-/immune-therapy targeting the amyloid clone is currently being tested in controlled clinical trials. Response to therapy is assessed based on validated criteria. Profound hematologic response is the early goal of treatment and should be accompanied over time by deepening organ response. Many relapsed/refractory patients are also treated with daratumumab combination, but novel regimens will be needed to rescue daratumumab-exposed subjects. Immunomodulatory drugs are the current cornerstone of rescue therapy, while immunotherapy targeting B-cell maturation antigen and inhibitors of Bcl-2 are promising alternatives.

1 Introduction

Systemic light chain (AL) amyloidosis is caused by a B cell clone producing a light chain that undergoes conformational changes and deposits in tissue in the form of amyloid fibrils [1]. This process causes progressive organ dysfunction and death if it is not arrested by effective therapy. The other most common form of systemic amyloidosis is caused by the deposition of transthyretin (both in its wild-type and mutated forms, ATTRwt and ATTRv, respectively). The clinical manifestations of AL and ATTR amyloidosis largely overlap, despite the biochemical and etiological differences [1]. In AL amyloidosis, the amyloid clone is most commonly formed of plasma cells (PCs) and it is generally small, with a median bone marrow plasma cell (BMPC) infiltrate of 10%. The amyloid PC clone shares characteristics found both in clones from patients with monoclonal gammopathy of uncertain significance (MGUS) and multiple myeloma (MM). For instance, in AL amyloidosis the mutational load is similar to that of MGUS and significantly lower than in MM [2]. In particular, the MM-driver genes are not recurrently mutated [3–5], and *t*(11;14) is the most common chromosomal abnormality (~50% of patients) and is associated with a lower frequency of subclones [6]. The use of certain light chain germline genes is associated with preferential organ involvement, with *IGLV6-57*, *IGLV1-44*, and *IGKV1-33* preferentially targeting the kidney, heart, and liver, respectively [7–9]. The ability of monoclonal light chains to form amyloid depends on mutations in the variable region, causing low-fold stability and high protein dynamics [10]. In recent years, cryogenic electron microscopy studies elucidated the structure of amyloid fibrils [11, 12] and showed that light chain aggregation involves extensive structural conversion of the variable region. Pre-clinical and clinical studies indicate that amyloid light chains directly impair cardiomyocyte function, linking improvement of cardiac

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Key Points

Early and accurate diagnosis and typing of AL amyloidosis are vital to grant patients access to specific treatment when organ damage is still reversible.

Treatment should be risk-adapted, based on international guidelines, and specific clonal features, such as translocation *t*(11;14) and gain 1q21, may guide treatment choice.

Hematologic response to therapy should be assessed early and frequently. In patients obtaining complete response, minimal residual disease (MRD) evaluation should always be suggested in order to guide future decision making.

Novel treatment approaches are under evaluation especially in the relapsed/refractory setting and international collaborations should be favored.

involvement to the level of the circulating amyloid precursor [13, 14]. This growing knowledge of disease mechanisms was accompanied by an even faster development of our practical ability to diagnose and treat patients with AL amyloidosis thanks to biomarkers of organ and clonal disease and to novel, powerful regimens that were tested in controlled clinical trials.

2 Diagnosis

Systemic AL amyloidosis manifests with signs and symptoms of organ involvement (Table 1). However, these manifestations are deceitful because they often mimic symptoms and signs of more common diseases and can be overlooked for several months even in patients known to have a preexisting plasma cell dyscrasia [15]. Yet, combinations of symptoms and signs related to different organs in the same patients can help identify the disease. The pathognomonic signs of amyloidosis can be identified only in a minority of cases and they often indicate advanced stages of the disease (Fig. 1). Based on the existence of a long pre-symptomatic phase, with elevated levels of amyloid free light chains (FLC) detectable in patients at least 4 years before the onset of symptoms of AL amyloidosis [16], we advocated a biomarker-based screening (especially N-terminal pro-natriuretic peptide type-B [NT-proBNP]) in patients known to have a monoclonal

gammopathy with altered FLC ratio [17, 18]. The identification of patients with pre-symptomatic AL amyloidosis before the onset of severe organ involvement may allow the delivery of more effective therapy, resulting in improved response rates and survival. The cost effectiveness of this approach has yet to be proven in a prospective setting.

The diagnosis of AL amyloidosis needs to be biopsy proven. Our diagnostic algorithm is depicted in Fig. 2. Amyloid deposits can be found at non-invasive biopsy sites in a substantial proportion of patients. For instance, abdominal fat aspiration, probably the most common diagnostic procedure, has a sensitivity of 80% in AL amyloidosis [19]. The combination of abdominal fat aspirate and Congo red staining of bone marrow biopsy approaches a diagnostic sensitivity of 90% [20]. The biopsy of minor salivary glands can find amyloid deposits in more than 50% of subjects with negative fat aspirates [21] and rectal biopsy may be also considered. However, when there is a strong clinical suspicion, the involved organ biopsy should be performed immediately in subjects with negative fat or bone marrow biopsies. Specific amyloid radiotracers are being developed that might become clinical tools to identify and localize amyloid deposits in patients [22]. A significant overlap of organ involvement and clinical manifestations exist between the most common forms of systemic amyloidosis [23]. Thus, once amyloid deposits are detected, unequivocal typing with adequate technology is mandatory to start the appropriate specific therapy. Although it has been proven that bisphosphonate scintigraphy tracers have a preferential uptake in the heart of patients with non-AL, most commonly transthyretin (ATTR), amyloidosis, substantial uptake can sometimes be found in the heart of patients with AL amyloidosis [24]. For this reason, the diagnosis of cardiac amyloidosis requires tissue typing in all patients in whom a monoclonal component is found (Fig. 2) [25]. Because AL amyloidosis is the form of cardiac amyloidosis with the most rapid progression (sometimes a matter of few weeks) and should be considered a medical emergency, when cardiac amyloidosis is suspected, looking for the presence of the amyloid clone should be the first step and should then direct the workup towards a biopsy-based or a possibly biopsy-free approach [23, 26]. However, the amyloid clone is usually small, and a combination of sensitive methods (immunofixation of serum and urine and measurement of FLC) should be employed to grant adequate sensitivity [27–30]. The International Society of Amyloidosis (ISA) recently surveyed the approach to tissue typing at referral centers emphasizing a still relevant heterogeneity of diagnostic approaches [31]. The Mayo Clinic researchers reported that the use of immunofluorescence in renal biopsies has inferior sensitivity and specificity compared with laser microdissection/mass spectrometry in the typing of AL amyloidosis [32]. Light microscopy immunohistochemistry

Table 1 Signs and symptoms of AL amyloidosis organ involvement

Organ involved	Signs and/or symptoms
Heart	Heart failure with preserved ejection fraction
	Thickened ventricular walls and low voltages on electrocardiography
	Fatigue
	Dyspnea at rest or exertion
	Hypotension (often postural)
	Syncope
	Peripheral edema
	NT-proBNP (or BNP) increase, confirmed by imaging (cardiac magnetic resonance imaging or echocardiographic)
Kidney	Peripheral edema
	Nephrotic range proteinuria
	Renal failure
Nervous system	*Autonomic*
	Postural hypotension
	Erectile dysfunction
	Alteration of gastrointestinal motility
	Gastro-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
	Peripheral
	Carpal tunnel syndrome (often bilateral)
	Symmetric lower extremity sensorimotor polyneuropathy (ascending, symmetric, small fiber/axonal)
Gastrointestinal tract	Bleeding (especially if factor X deficiency associated)
	Malabsorption
	Weight loss
	Diarrhea
Liver	Hepatomegaly
	Increased alkaline phosphatase
Soft tissue	Macroglossia
	Claudication, presumed vascular amyloid
	Periorbital purpura
	Submandibular enlargement/gland swelling

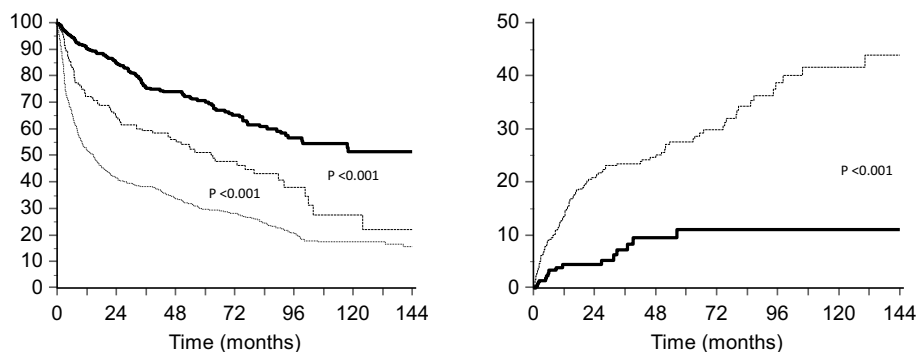AL systemic light chain, *NT-proBNP* N-terminal pro-natriuretic peptide type-B

Fig. 1 A Overall survival according to the presence of symptomatic organ involvement. Continuous line—no heart involvement ($N = 240$), median survival 151 months. Dotted line—asymptomatic heart involvement ($N = 215$), median survival 63 months. Small-dot line—symptomatic heart involvement ($N = 835$), median survival 15 months. **B** Renal survival according to the presence of symptomatic renal involvement. Plane line—asymptomatic renal involvement (proteinuria <3 g/24 h), $N = 578$, dialysis 21% @ 2 years, 28% @ 5 years. Dotted line—symptomatic renal involvement (proteinuria >3 g/24 h), ($N = 578$): dialysis 21% @ 2 years, 28% @ 5 years. Data reported are from the prospectively maintained database from the Pavia Amyloidosis Center
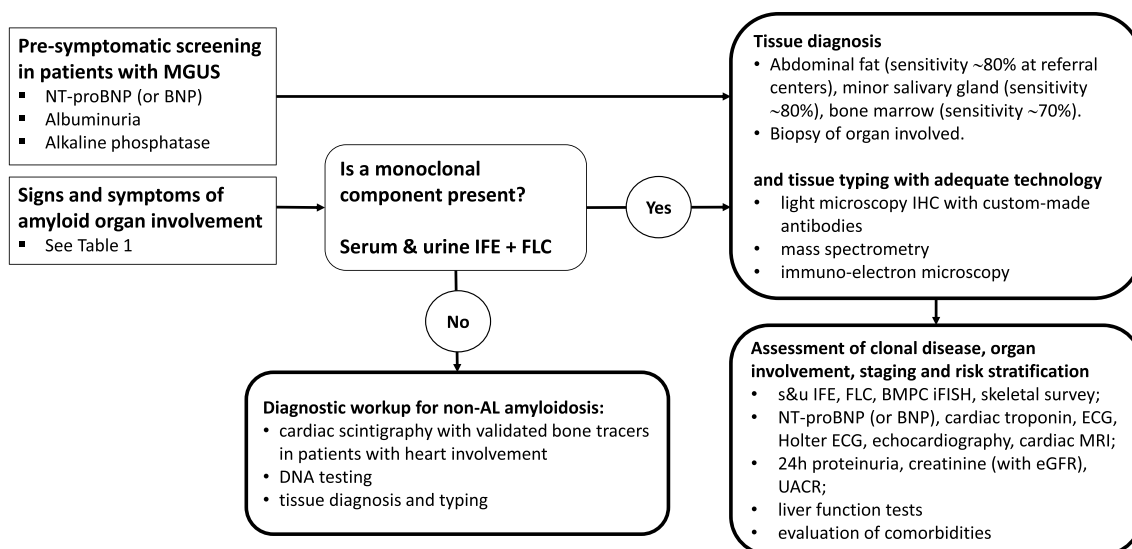
Fig. 2 Diagnostic algorithm for the diagnosis of systemic amyloidosis. *BMPC* bone marrow plasma cell infiltrate, *eGFR* estimated glomerular filtration rate, *IFE* immunofixation, *FLC f*ree light chain, *UACR* urinary albumin to creatinine ratio

with commercial antibodies lacks specificity and can lead to dangerous mistyping [33, 34]. Thus, light chain microscopy immunohistochemistry grants adequate diagnostic accuracy only when performed with amyloid-specific antibodies [31, 35]. Commercial antibodies can be reliably employed with electron microscopy allowing to correctly classify > 99% of patients [19]. Mass spectrometry-based typing is not antibody-dependent and can be performed after laser capture microdissection of relevant amyloid-rich tissue areas or on whole tissue and is currently considered the gold standard for amyloid typing [36, 37].

In patients with a positive biopsy, organ involvement is defined by clinical chemistry testing and cardiac imaging. Albuminuria followed by progressive reduction of estimated glomerular filtration rate (eGFR) reveals renal involvement and increased levels of cholestasis markers uncover liver involvement. In patients with heart involvement, echocardiography can detect increased ventricular wall thickness with preserved ventricular size and atrial enlargement, reduced left ventricular global longitudinal strain (GLS) with preserved apical strain (basal-apical gradient), diastolic dysfunction, valve thickening, atrial septum hypertrophy, and mild pericardial and pleural effusions. Cardiac magnetic resonance shows diffuse or patchy subendocardial or transmural pattern late gadolinium enhancement (LGE), atrial LGE, abnormal myocardium and blood-pool gadolinium kinetics, increased native T1 mapping values, and elevated extracellular volume fraction.

Prognostic stratification is performed with accurate biomarker-based staging systems that sharply discriminate patients with different outcomes (Table 2) [38–45]. While patients diagnosed at early stages of cardiac and renal

involvement can enjoy prolonged survival and avoid endstage renal disease, subjects with advanced heart involvement (stage IIIb with the Mayo Clinic/European staging system) have a median survival of only a few months.

3 Therapy

3.1 Upfront Therapy

The treatment of patients with AL amyloidosis has long been based on retrospective series and expert opinions, with very few controlled studies. It is only in the last couple of years that two large Phase III trials proved that bortezomib-based therapy is superior to the old standard of care and that the addition of daratumumab further improves the outcomes (Table 3). These studies were made possible by the availability of validated criteria of hematologic response [46, 47] that were used as primary endpoints, as well as of cardiac [46, 48] and renal [43–45] response (Table 4). These biomarker-based response criteria can be used early (1 to 6 months) after treatment initiation [49–51] and consistently predict survival and time to dialysis.

In an international academic study, melphalan dexamethasone (MDex) was compared to MDex with the addition of bortezomib (BMDex) [52]. The three-drug combination granted more frequent and deeper hematologic responses and prolonged overall survival. More recently, a large Phase III trial showed that the combination of daratumumab, cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) granted significantly higher rates of hematologic and organ responses than CyBorD alone [53]. Importantly,

the rate of complete hematologic response (CR) was unprecedentedly high (54%) with Dara-CyBorD. Based on these results Dara-CyBorD became the new standard-of-care and the first licensed combination for AL amyloidosis.

A Phase III trial published in 2007 compared autologous stem cell transplantation (ASCT) with MDex and showed no benefit for ASCT [54]. However, this study was conducted with an outdated comparator and was performed before the eligibility criteria for ASCT were refined with the introduction of cardiac biomarkers. The use of these criteria resulted in substantially decreased transplant-related mortality (TRM). It is now clearly recognized that patients with elevated N-terminal pro-natriuretic peptide type-B (NT-proBNP) and troponin should not be transplanted because they are at very high risk of death [55]. With refined eligibility criteria, TRM can be as low as 2–3%, and the hematologic response rate to ASCT (overall 84%, CR 39%, very good partial response [VGPR] 33%) is remarkable [56]. Moreover, we have a large series of transplanted patients with a very long follow-up and we know that hematologic response to ASCT is durable [57], while we still lack these data for newer non-transplant approaches.

Based on this evidence, the International Society of Amyloidosis (ISA) and the European Hematology Association (EHA) recently issued guidelines for the treatment of AL amyloidosis [58, 59]. The first step in the design of the therapeutic strategy should be to assess the eligibility to ASCT based on age, cardiac biomarkers, and kidney and respiratory function. The ISA/EHA eligibility criteria are reported in Table 5. Transplant should be preceded by induction with Dara-CyBorD or CyBorD alone. Induction therapy improves the response rate in patients who have a BMPC infiltrate >10% [60]. Moreover, induction therapy may render eligible to ASCT subjects whose heart involvement was originally too advanced [61]. In addition, induction therapy alone may be enough to grant a durable and satisfactory response [62]. At our center, we offer ASCT-eligible patients a sequential treatment approach, offering transplant only to subjects who do not attain CR or VGPR after induction. With this strategy, hematologic response rate is high (overall 76%, CR 34%, VGPR 29%), median duration of response is 4.5 years, and TRM is less than 1% [62].

Patients who are not transplant candidates should receive Dara-CyBorD. Where daratumumab is still unavailable, CyBorD or BMDex are viable alternatives. Patients whose clones harbor the translocation (11;14) have poorer outcomes with bortezomib, but not when melphalan and daratumumab are used [63]. The recent ISA guidelines recommended a reduction of the bortezomib dose in stage IIIb patients. In these patients, single agent daratumumab is an appealing option and is currently being tested in a European Phase II study [64]. Bortezomib may not be safely employed in patients with relevant peripheral neuropathy or pulmonary fibrosis. Different case reports and small series reported a possible association of bortezomib-based treatment and pulmonary fibrosis [65, 66]. If daratumumab is not accessible as a single agent, MDex or lenalidomide combinations can be considered in these subjects. In previously untreated patients, the overall hematologic response rate to the combination of cyclophosphamide, lenalidomide, and dexamethasone is 46% (CR 25%, VGPR 18%) [67].

Patients with an underlying IgM-producing lymphoplasmacytic clone (approximately 5%) need a different approach. The ISA/EHA guidelines recommend the combination of rituximab and bendamustine in these patients [59]. Overall, 60% of patients respond to this combination (CR 14%, VGPR 32%) [68]. Rituximab can also be combined with cyclophosphamide or bortezomib [69], and the latter may be suitable for patients harboring clones with both PC and lymphoplasmacytic phenotype. Ibrutinib appears to have a significant toxicity in patients with AL amyloidosis and should be used with caution [70]. The use of other BTK inhibitors has not been yet evaluated in AL amyloidosis and needs further investigation, especially for the lower rate of cardiac effect reported [71].

All these approaches aim to reduce the supply of the amyloid precursor. Passive immunotherapy with monoclonal antibodies is being explored to promote resorption of the amyloid deposits [72]. For now, this strategy has met with limited clinical success. The clinical development of dezamizumab, a monoclonal antibody targeting serum amyloid P component (SAP), combined with the circulating SAP-depleting small molecule miridesap, is expected to remove SAP from amyloid fibrils; thus, exposing them to degradation, was interrupted due to an unfavorable risk/benefit ratio [73]. Birtamimab targets a conformational epitope in serum amyloid A (cross-reacting with misfolded light chain). After encouraging results from an uncontrolled study showing organ responses in patients receiving the antibody after chemotherapy, two controlled study of birtamimab combined with chemotherapy or in chemotherapy-exposed patients were interrupted for futility. Yet, a post hoc analysis showed that revised Mayo Clinic stage IV patients with NT-proBNP ≤ 8500 ng/L receiving birtamimab with chemotherapy had a better outcome than controls [74]. A new controlled study combining birtamimab and anti-PC treatment in this specific population is underway (NCT04973137). Finally, a recent Phase I study of anselamimab (CAEL-101), showed cardiac responses in patients receiving the antibody after chemotherapy [75]. Based on this encouraging observation, two controlled clinical trials are underway to assess the efficacy of anselamimab in combination with chemotherapy in patients with Mayo Clinic/European stage IIIa (NCT04512235) and IIIb (NCT04504825) AL amyloidosis.

3.2 Assessment of Response and Progression

The outcome of patients with AL amyloidosis is tightly linked to the depth and speed of FLC reduction. The evaluation of hematologic response is crucial for the subsequent treatment decision making. It is now widely accepted that at least VGPR should be reached early after treatment initiation, ideally within the first month [49, 50]. This early and deep response can improve the outcome in patients with very advanced, stage IIIb heart involvement [49, 51]. Patients who do not attain a hematologic response within 2 months and VGPR within 4 months should be considered refractory and offered rescue therapy [76]. Upfront therapy should be continued until hematologic response plateaus and consolidation with 2 additional cycles is generally recommended. There is no evidence in favor of maintenance therapy in AL amyloidosis with the non-daratumumab-based treatment approaches. Moreover, treatment with daratumumab is generally offered after Dara-CyBorD based on the ANDROMEDA study design, even if the maintenance part of the trial had no comparator arm [53]. Daratumumab maintenance treatment also seems reasonable in patients with large, myeloma-like clones [26].

Organ response depends on the quality of hematologic response. It can appear as early as 3 months after treatment initiation even in patients with advanced disease [51], and its frequency and depth continues to improve over time if hematologic response is maintained. Sometimes, organ response is not attained even in patients with hematologic CR. This might be due to irreversible organ involvement or persistent amyloid deposits. Yet, emerging evidence suggests that the rate of organ response may exceed 90% in subjects in CR with undetectable minimal residual disease (MRD) [77–79]. These observations emphasize the role of minimal, even undetectable amounts of circulating amyloid light chains in preventing recovery of organ dysfunction. Also, continuous improvement up to normalization of organ involvement reveals that the level of hematologic response is able to invert the course of the disease. Indeed, it has been shown that organ response can be graded similar to hematologic response, and depth of organ response is associated with improved survival [80, 81].

While we have validated measures of organ response that are largely used in individual patient management and as endpoints in clinical trials, we lack a validated definition of progression. The current definitions of cardiac and renal progression are associated with reduced survival and a higher rate of dialysis, respectively, and therefore cannot be used to trigger rescue treatment [43, 46]. There is no agreement on which level of increase of FLC concentration should be considered enough to start second-line therapy [82–84]. Yet, even small increases can precede ominous progression of organ dysfunction [85].

In an attempt to better understand the mechanisms of cardiac involvement and to provide additional endpoints for clinical trials that do not rely on cardiac biomarkers, other tools are currently being explored as measures of improvement of heart involvement in AL amyloidosis, but to date, none have been validated in independent series. For instance, a ≥ 33 m improvement in 6-minute walk test (6MWT) at 12 months correlates with hematologic response and predicts survival [86]. However, 6MWT improvement is rarely observed at earlier timepoints, possibly because of the effects anti-PC therapy. Global longitudinal strain (GLS) is an echocardiographic measure of left ventricular systolic function. An improvement of GLS of at least -2% at 12 months was associated with the depth of hematologic response and predicted survival improving the discriminating ability of NT-proBNP response [87]. Reduction of extracellular volume (ECV) by at least 5% at cardiovascular magnetic resonance (CMR) is associated with hematologic and NT-proBNP response and predicts survival [88]. It is rarely (3% of patients) observed at 6 months, and its frequency increases with time after anti-PC therapy. One common limitation of these new proposed measures of cardiac response is that they only become relevant after a long period of time (12 months) after treatment initiation, thus limiting their usefulness in early assessment of treatment efficacy and as endpoints in clinical trials.

3.3 Treatment of Relapsed and Refractory Patients

The choice of rescue treatment of patients with AL amyloidosis was also addressed in the ISA/EHA guidelines [59] and considers exposure and response to agents used up-front (summarized in Fig. 3). These indications are based on several large retrospective series and small Phase II studies. If hematologic response was prolonged, re-challenge with effective agents used up-front seems reasonable. Compared with switch to a different approach this is associated with shorter progression-free but not overall survival [89].

Only one controlled clinical trial has been performed in the relapsed/refractory setting. The study compared ixazomib-dexamethasone with physician's choice (which was lenalidomide-based in 57% of cases) [90]. Unfortunately, the study failed to meet its primary endpoint, overall hematologic response at 3 months (53% with ixazomib and 51% in the comparator arm). Hematologic response rate to ixazomib tended to be higher in proteasome inhibitor-naïve patients (63% vs 41%, CR 33% vs 18%). Cardiac (18% vs 5%) and renal (28% vs 7%) responses were more frequent, and time to next treatment was significantly longer in patients treated with ixazomib, but there was no difference in overall survival. Immunomodulatory drugs are still the cornerstone of rescue therapy, but deep hematologic responses are rare. The combination of lenalidomide and dexamethasone was
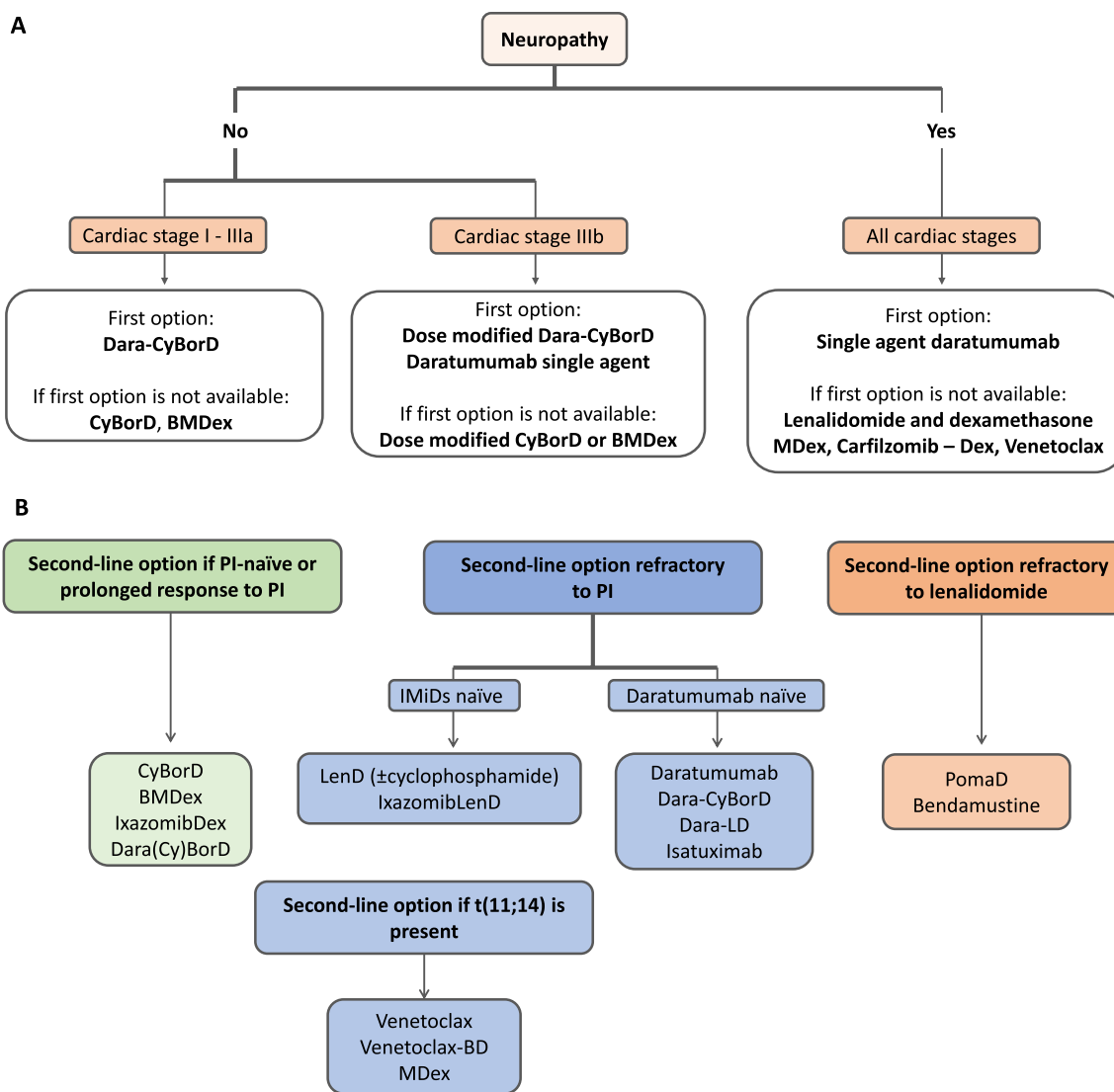
A

Fig. 3 **A** ISA/EHA guidelines for the treatment of newly diagnosed AL amyloidosis patients. **B** ISA/EHA guidelines for the treatment of relapsed/refractory systemic light chain (AL) amyloidosis patients. *BD* bortezomib, dexamethasone, *BMDex* bortezomib, melphalan, dexamethasone, *CyBorD* cyclophosphamide, bortezomib, dexametha- sone, *Dara* daratumumab, *IMiDs* immunomodulatory drug, *LenD* lenalidomide and dexamethasone, *MDex* melphalan and dexametha- sone, *PI* proteasome inhibitor, *PomaD* pomalidomide, dexametha- sone. Adapted from Wechalekar et al Amyloid 2022 [59]

reported to grant a hematologic response in 31% of patients (CR 5%, VGPR 15%) in a recent large retrospective study [91]. Lenalidomide should be used with caution in AL amy- loidosis. The maximum tolerated dose is 15 mg/day, and this drug is associated with eGFR decrease in patients with proteinuria from amyloid renal involvement [92]. A large European retrospective study showed that pomalidomide and dexamethasone grant a hematologic response of 44% (CR 3%, VGPR 23%) in heavily pretreated subjects who were mostly refractory to bortezomib and lenalidomide [93]. A possible advantage of pomalidomide compared to lena- lidomide is the possible use in patients with advanced renal failure. Immunomodulatory drugs are associated with an

increase in cardiac biomarkers and possible IMID-induced fluid retention that interferes with cardiac response assess- ment [94].

Daratumumab has been extensively used, either alone or in combination, in the relapsed/refractory setting. However, the Heidelberg and Boston University groups independently reported a detrimental effect on response rates and survival of amp(1q21) in patients treated with daratumumab as res- cue therapy [95–97]. Daratumumab monotherapy was tested in 2 independent Phase II trials that gave discordant results in terms of hematologic response: 90% (CR 41%, VGPR 45%) and 55% (CR 8%, VGPR 40%) in the Boston Uni- versity and European studies, respectively [98, 99]. This

Table 2 Staging systems for AL amyloidosis

Staging system	Markers and thresholds	Stages
Cardiac (NT-proBNP based) [38, 39]	NT-proBNP > 332 ng/L	I. No markers above the cutoff
	cTnT > 0.035 ng/mL(or cTnI > 0.01 ng/mL or hs-cTnT >50 ng/L)	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
Revised Mayo Clinic [42]	NT-proBNP > 1800 ng/L	I. 0 markers above the cutoff
	cTnT > 0.025 ng/mL(or hs-cTnT > 50 ng/L)	II. One marker above the cutoff
	dFLC > 180 mg/L	III. Two markers above the cutoff
		IV. Three markers above the cutoff
Cardiac (BNP based) [41]	BNP > 81 ng/L	I. No markers above the cutoff
	cTnI > 0.1 ng/mL	II. One marker above the cutoff
		IIIa. Both markers above the cutoff and BNP <700 ng/L
		IIIb. Both markers above the cutoff and BNP ≥700 ng/L
Renal (24-h proteinuria based) [43]	eGFR ≤ 50 mL/min per 1.73 m^2	I. Both eGFR above and proteinuria below the cutoffs
	Proteinuria ≥ 5 g/24 h	II. Either eGFR below or proteinuria above the cutoffs
		III. Both eGFR below and proteinuria above the cutoffs
Renal (UACR based) [45]	eGFR ≤ 50 mL/min per 1.73 m^2	I. Both eGFR above and UACR below the cutoffs
	UACR ≥ 3600 mg/g	II. Either eGFR below or UACR above the cutoffs
		III. Both eGFR below and UACR above the cutoffs

cTnI cardiac troponin I, *cTnT* cardiac troponin T, *dFLC* difference between involved (amyloidogenic) and uninvolved circulating free light chain, *eGFR* estimated glomerular filtration rate, *hs-cTnT* high sensitivity cardiac troponin T, *NT-proBNP* N-terminal pro-natriuretic peptide type-B, *UACR* urinary albumin/creatinine ratio

discrepancy was probably due to a higher proportion of refractory subjects in the latter trial. Patients who did not receive bortezomib up-front can be offered daratumumab-bortezomib combinations. This combination is highly effective in daratumumab-naïve subjects, granting a hematologic response in 66% of patients (CR 11%, VGPR 55%) [95]. Daratumumab can be combined with lenalidomide in subjects who received bortezomib up-front. A large retrospective study showed that this combination is very effective (hematologic response 84%, CR 16%, VGPR 65%) [96].

Patients whose amyloid clones harbor the translocation (11;14) can be very effectively treated with venetoclax. This drug was reported to grant a VGPR or better in almost 80% of patients with AL amyloidosis and a *t*(11;14) [100].

Besides daratumumab, other immunotherapy approaches are being explored in patients with relapsed/refractory AL amyloidosis. Isatuximab was tested in a Phase II study and the first analysis was presented in 2020 [101]. No data are yet available regarding the use of this approach in daratumumab refractory patients. Belantamab mafodotin is a monoclonal antibody targeting the B-cell maturation antigen (BCMA) conjugated to a microtubule-disrupting agent, monomethyl auristatin F. Two recent independent retrospective reports found a total of 17 patients, 12 (71%) of whom responded and 7 (41%) attained CR [102, 103]. In addition, treatment with chimeric antigen receptor T (CAR-T) cells targeting BCMA has been attempted in heavily pretreated patients with AL amyloidosis. All the 5 treated patients achieved hematologic CR and organ response [104, 105]. Bi-specific antibody approaches are under investigation in AL amyloidosis (i.e., NCT04557098).

4 Conclusions and Future Directions

Over the last decades, our understanding of the mechanisms of AL amyloidosis has steadily improved, inspired by clinical observation. We have now identified several relevant targets in the amyloid cascade that will be targeted by future therapeutic approaches. Validated response criteria based on biomarkers allowed the completion of meaningful clinical trials, and for the first time we have a licensed regimen for AL amyloidosis. There is hope to go beyond anti-clone therapy, becoming able to target the deposits with passive immunotherapy and possibly stabilizing the amyloid light chain with small molecule, as was effectively done in transthyretin amyloidosis [106].

Yet, many unmet needs remain that should be addressed by future action.

Table 3 Outcomes of the recent Phase III trial in AL amyloidosis

Regimen	Patients and staging	Hematologic response	Organ response
MDex [52]	Total: 56	Overall: 57%	Heart: 22%
	Stage I: 13%	CR: 20%	Kidney: 43%
	Stage II: 70%	VGPR: 19%	
	Stage IIIa: 17%	PR: 18%	
	Stage IIIb: 0%		
BMDex [52]	Total: 53	Overall: 81%	Heart: 38%
	Stage I: 13%	CR: 23%	Kidney: 39%
	Stage II: 70%	VGPR: 41%	
	Stage IIIa: 17%	PR: 17%	
	Stage IIIb: 0%		
CyBorD [53]	Total: 193	Overall: 77%	Heart: 22%
	Stage I: 22%	CR: 27%	Kidney: 24%
	Stage II: 42%	VGPR: 22%	
	Stage IIIa: 33%	PR: 28%	
	Stage IIIb: 3%		
Dara-CyBorD [53]	Total: 195	Overall: 92%	Heart: 42%
	Stage I: 24%	CR: 54%	Kidney: 53%
	Stage II: 39%	VGPR: 25%	
	Stage IIIa: 36%	PR: 13%	
	Stage IIIb: 1%		

BMDex bortezomib, melphalan, and dexamethasone, *CR* complete response, *CyBorD* cyclophosphamide, bortezomib, and dexamethasone, *Dara-CyBorD* daratumumab, cyclophosphamide, bortezomib and dexamethasone, *MDex* melphalan and dexamethasone, *PR* partial response, *VGPR* very good partial response.ggh

Staging is classified according to the Mayo Clinic / European system [40]. Hematologic and organ responses are defined according to the International Society of Amyloidosis criteria [43, 46, 47].

Table 4 Validated hematologic and organ response criteria for AL amyloidosis

Response categories	Criteria definition
Hematologic response	**References** [46, 47]
Complete response (aCR)	*Both criteria must be met:*
	Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative immunofixation electrophoresis of both serum and urine
	Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio
Very good partial response (VGPR)	dFLC concentration <40 mg/L
Partial response (PR)	dFLC decrease >50% compared to baseline
Stable / No response	All other patients
Cardiac Response	**References** [46, 48]
NT-proBNP response	30% and > 300 ng/L NT-proBNP decrease if baseline NT-proBNP ≥ 650 ng/L
BNP response	30% and > 50 ng/L BNP decrease if baseline BNP ≥ 150 ng/L
Renal response	**References** [45, 43]
Renal response (24-h proteinuria)	≥30% decrease in proteinuria or drop of proteinuria below 0.5 g/24h in the absence of renal progression (defined as ≥25% decrease in eGFR)
Renal response (UACR)	≥30% decrease in UACR without ≥25% decrease in eGFR

dFLC difference between amyloidogenic (involved) and non-amyloidogenic (uninvolved) free light chain concentrations, *eGFR* estimated glomerular filtration rate, *FLC* free light chains, *M component* monoclonal component

Table 5 Eligibility criteria for autologous stem cell transplant in AL amyloidosis [58]

Inclusion criteria	Exclusion criteria
Between 18 and 65 years (patients aged 66–69 years can be considered at referral centers after careful multidisciplinary discussion)	Symptomatic and/or medically refractory ventricular and atrial arrhythmias
Supine SBP at least 90 mmHg	Uncompensated heart failure
Performance status (ECOG) 0–2 (unless caused by peripheral neuropathy)	Orthostatic hypotension refractory to medical therapy
NYHA class I or II	Symptomatic and/or medically refractory pleural effusions
Cardiac stage I or II (cardiac stage III patients can be considered at referral centers after careful multidisciplinary discussion)	Extensive GI involvement with evidence of active GI bleeding or risk of bleeding
Biomarkers:	
NT-proBNP less than 5000 ng/L	Factor X deficiency with factor X level of less than 25% or/and evidence of active bleeding
Troponin I less than 100 ng/L or troponin T less than 60 ng/L or hs-troponin T less than 75 ng/L	
Direct bilirubin <2 mg/dL	
eGFR greater than 50 ml/min/1.73 m^2 (patients whose eGFR is between 50 and 30 mL/min can be considered at referral centers after careful multidisciplinary discussion)	
Patients on chronic and stable schedule of dialysis should not be excluded	
Oxygen saturation of at least 95% on room air. DLCO greater than 50%	

DLCO diffusion capacity of carbon monoxide, *ECOG* Eastern Cooperative Oncology Group, *eGFR* estimated glomerular filtration rate, *GI* gastro-intestinal, *hs* high sensitivity, *NT-proBNP* amino-terminal pro-natriuretic peptide type-B, *NYHA* New York Heart Association, *SBP* systolic blood pressure

– First, we are still diagnosing this disease late and we need to increase our efforts to detect AL amyloidosis at earlier, possibly pre-symptomatic stages. A screening program in patients with monoclonal gammopathy of undetermined significance could be implemented.

– The access to adequate technologies for amyloid diagnosis and typing should be improved by favoring the access of patients to specialized centers directly, through networks, and possibly through tele-consultations.

– The availability of highly effective treatments raises the question on the accuracy and sensitivity in evaluating hematologic and organ response. Particularly, the presence of MRD should be tested in prospective clinical trials and the most appropriate methodology and timing for MRD assessment should be defined.

– We are still lacking validated criteria for progression. This is relevant for individual patient management and time to event point in clinical trial design. Identification and validation in an international setting are warranted.

– In the near future we will be confronted with an increasing number of patients relapsing after or refractory to daratumumab, and clinical trials (with Bcl-2 inhibitors, bi-specific antibodies and alternative immunotherapy including CAR-T cells) should be designed to address this need.

These goals can be achieved by transparent cooperation of patients, academia, regulatory agencies, pharma companies, and non-for-profit organizations each in their specific role.

Declarations

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