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# Systemic AL Amyloidosis: Current Approaches to Diagnosis and Management

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**Abstract**

AL amyloidosis is characterized by a low-level expansion of an indolent, small plasma cell clone that produces amyloidogenic light chains. Amyloid aggregates or preceding intermediaries cause direct cell damage through their proteotoxicity, and amyloid deposits distort tissue architecture, and, eventually, lead to organ impairment. It is a rare, underdiagnosed disease with a diverse clinical presentation depending on the organ tropism of the amyloid fibrils; cardiac and renal involvement is most common, but any organ can be affected, excluding the central nervous system. A high level of awareness and a systematic approach using newly emerging screening biomarkers is required to achieve early diagnosis. Management should be multidisciplinary as supportive management tailored to management of organ dysfunction is paramount to survival and minimization of treatment-associated toxicity. The initial therapeutic aim is to rapidly eliminate the clonal plasma cell that produces the circulating amyloid precursor and achieve a complete hematologic response, and if possible with undetectable minimal residual disease as assessed by next-generation methods (flow and sequencing), with minimal toxicity. Treatment is tailored to the initial risk assessment of the patients. Treatments are based on regimens adapted from the expanding options that are available for multiple myeloma patients and hematological response rates have improved. Organ response rates are strongly associated with deeper hematologic response but usually lag behind hematological response and are also dependent on the initial organ function reserve. Agents directed against the amyloid deposits have been explored to aid amyloid clearance and improve organ function, but data are still negative.

## Introduction

Amyloidosis is a collective term for a diverse group of diseases characterized by misfolding of soluble precursor proteins, eventually forming highly ordered amyloid cross β-fibrils which deposit in various tissues. Amyloid aggregates and their preceding intermediaries can cause proteotoxic intracellular stress and direct cell damage leading to apoptosis, while amyloid fibril deposits disrupt tissue architecture, leading to progressive failure of affected organs.[1] In immunoglobulin light chain (AL) amyloidosis, clonal plasma/B-cells produce the amyloid, which is an immunoglobulin light chain. The clinical presentation depends on the type and extent of organ involvement; the heart and the kidney are affected most commonly, followed by the autonomic nervous system, the liver, the gastrointestinal tract, and soft tissues. Median age at diagnosis is about 63 years and incidence increases with age. Given the rarity of the disease and the difficulties in diagnosis, there are no reliable large population registries to derive accurate incidence and prevalence. Estimated incidence ranges around 10 to 12 cases per million person-years,[2] which corresponds to about 1 to 2 patients with AL amyloidosis for every 10 patients diagnosed with myeloma. Therapy targeting the aberrant plasma/B-cell clone is the mainstay of treatment in AL amyloidosis. The increasing number of different anti-clonal agents that have been developed for the treatment of multiple myeloma (MM) and have been adopted and adapted for patients with AL amyloidosis, have improved survival: in a recent single center review, 2-year survival increased to 60% over the 2010 to 2014 period compared with 42% over 2000 to 2004.[3] Prevalence has also increased, probably secondary to prolonged survival and improved diagnostic means.[2,3,4] The disease is, however, incurable and remains fatal, especially when the diagnosis is made late.

The current review will appraise data on the diagnostic approach, risk stratification and management of patients with AL amyloidosis, aiming to spotlight the need for increased awareness, systematic but targeted screening, and earlier diagnosis, patient and risk-tailored treatment and response-adapted strategies at all stages.

## Biology of AL amyloidosis

### The clone

The plasma cell (PC) clone in AL amyloidosis is usually small and indolent, secretes λ light chain in 75% to 80% of cases and

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shares phenotypic and copy number alterations with those observed in MM clones.[5] Studies using next-generation sequencing have shown that the patterns of mutations seen in AL clones fall between those found in MM and monoclonal gammopathy of undetermined significance (MGUS). A pre-existing monoclonal gammopathy is one of the most recognized risk factor for development of AL: MGUS increases the relative risk 8.8-fold compared to individuals without known MGUS.[6] It is estimated that approximately 15% of patients with MM have coexisting AL amyloidosis, and that 1% will develop AL amyloidosis during their disease course.[7] Single nucleotide polymorphisms (SNPs) at 10 particular loci have also been recognized as risk factors for AL, with the variant rs9344 within the splice site of CCND1, which encodes cyclinD1 and promotes the chromosomal t(11;14) translocation reaching the highest significance. Indeed, about 40% to 60% of patients with AL amyloidosis carry t(11;14) in their plasma cells, which is associated with worse outcomes in AL amyloidosis patients treated with bortezomib-based or immunomodulatory-based regimens.[8] About one quarter of patients will have gain/amplification of 1q21, with worse outcomes when treated with melphalan.[9] The presence of trisomies (seen in about 26% of patients) correlates with inferior overall survival (OS) following treatment with high dose melphalan (HDM). Cytogenetic abnormalities that have a clear adverse impact in MM patients (t(4;14), del17p, t(14;16)) are uncommon in AL.[8-10]

### Amyloidogenesis of the light chain

Compared to the light chain that is secreted in MM, the amyloidogenic light chain has lower fold stability and increased protein dynamics secondary to mutations in IGLV genes, which encode for the variable region of the light chain.[11] Soluble oligomers and amyloid fibrils are therefore formed. Amyloid fibrils cause disruption of tissue architecture and perturbate cellular membranes. Increased oxidative stress and proteotoxicity occur secondary to the effects of the amyloid oligomers.[12] Eventually, intracellular accumulation of oligomers and fibrils leads to cellular death. At the same time, processes of normal proteostasis are disrupted or overwhelmed.[13] Almost any organ or tissue may be affected. The light chain variable region (IGLV) gene family of the involved clone plays a role in organ tropism.[14] Post translational modifications are also important; it has been recognized that the clonal light chains in amyloidosis show high levels of N-glycosylation and dimerization.[15,16]

## Clinical presentation and diagnostic approach

### Who to search for AL amyloidosis?

The most crucial factor for the diagnosis of amyloidosis is disease suspicion. The heterogeneity of the clinical presentation of the AL patient is depicted in Figure 1. Most symptoms are non-specific, the diagnosis is often missed and delayed diagnosis is associated with early mortality due to end-stage dysfunction of target organ(s).[17] There are no specific biomarkers to diagnose or predict amyloidosis. N-glycosylation and dimerization of the monoclonal LC could be a marker to identify patients with monoclonal gammopathy at higher risk of developing AL amyloidosis.[15,16] Screening of the general population is discouraged due to very low sensitivity and specificity. However, targeted screening of at-risk populations may be relevant. Careful evaluation of the reported symptoms and follow-up of specific biomarkers at regular intervals has been proposed for individuals with MGUS/SMM with an abnormal FLC ratio. NT-proBNP increases at early stages of cardiac involvement and mild proteinuria may be the first symptom of renal involvement.[18] The sensitivity of these two in detecting early organ damage is high[19,20] but their specificity remains low. Clinical symptoms and signs that should raise suspicion include cardiac failure with preserved EF, nephrotic range proteinuria, bilateral carpal tunnel syndrome, axonal peripheral neuropathy or symptoms of autonomic dysfunction (Fig. 1).

### How to establish the diagnosis of AL amyloidosis

A condensed workflow of the recommended assessments for suspected AL amyloidosis is shown in Figure 2. A critical node in the diagnostic workflow is the identification of monoclonal immunoglobulin, for which all available techniques (serum and urine immunofixation, serum free light chains) should be combined.[21] Serum mass to detect a monoclonal immunoglobin may add sensitivity but its availability is limited.[22]

The diagnosis of AL amyloidosis requires biopsy-proven amyloid fibril detection; Congo red remains the most common staining method to detect amyloid, which is seen as green birefringent areas under polarized light microscopy. The site of biopsy can be a peripheral tissue (abdominal fat aspirate, salivary gland, etc) or an affected organ (kidney, liver, heart, stomach, etc). The choice of the site depends on the center's experience and preferences. Peripheral tissue biopsy is fast, easy, safe and inexpensive with reasonable sensitivity. Target organ biopsy has high sensitivity but requires expertise, has risks (bleeding, perforation, etc) and often causes significant delays.[23] False negative biopsies are not uncommon; persistence is key to diagnosis when clinical suspicion is high and repeat biopsy at an alternate site increases the probability of amyloid detection.[24] Positive Congo red alone in fat aspirate/biopsy or the BM in patients with monoclonal gammopathies without systemic symptoms, should not confer the diagnosis of "systemic AL amyloidosis". In the absence of symptoms or biomarker increase, the probability of developing AL amyloidosis is very low.[25] The probability of false positive tests (secondary to technical issues or in fat aspirates from diabetic patients using insulin) should also be kept in mind.[24,26] Following detection, typing of the amyloid is required to set the correct diagnosis. Available methods include immunohistochemistry (not optimized, requires a highly specialized pathology lab, 75% to 80% sensitivity, 80% specificity),[27] immunoelectron microscopy (100% specificity, 75% to 80% sensitivity, not widely available) and mass spectrometry (gold standard, reaching 100% specificity and ~95% sensitivity but available in very few centers worldwide).[27,28]

Systemic from localized amyloidosis should also be differentiated. Isolated amyloid deposits can be found in the skin, bladder, urinary tract, larynx, stomach, colon, lung, eyelids, etc.[29] Excluding systemic disease with prudent use of invasive tests is recommended. These patients have excellent prognosis and in most cases only local treatment is given (usually surgery or radiation).

The major disease to differentiate from AL amyloidosis, is ATTR-related cardiomyopathy, and mostly wild type (ie, non-hereditary) ATTR (ATTRwt) which affects mostly older patients (median age >70 years). The prevalence of MGUS increases with age but is higher than expected in patients with ATTRwt (10%–25%).[4,30] Caution is required to avoid a misdiagnosis of AL amyloidosis leading to anti-clonal treatment. $^{99m}$Tc-labeled pyrophosphate (PYP) or $^{99m}$Tc-labeled 3,3-diphosphono-1,2 propanodicarboxylic acid (DPD) scintigraphy detects tracer accumulation in the myocardium with high specificity for the

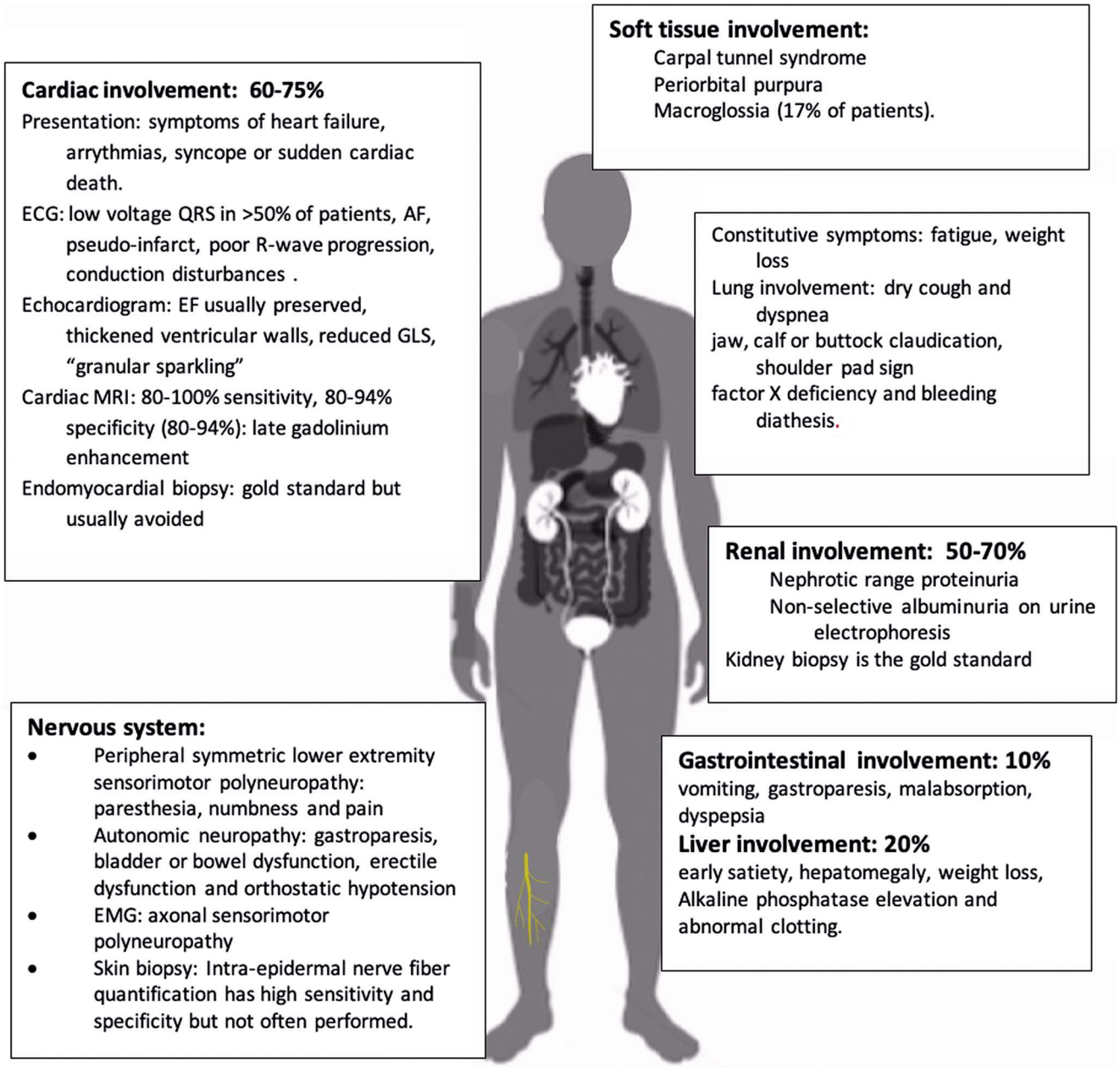


**Figure 1. Organ involvement and clinical presentation in AL amyloidosis**. AF = atrial fibrillation, ECG = electrocardiogram, EF = ejection fraction, EMG = electromyography, GLS = global longitudinal strain, MRI = magnetic resonance imaging.

diagnosis of ATTR, but only in the absence of monoclonal immunoglobulin. A subset of AL amyloidosis patients will have cardiac uptake of the bone tracers, thus, a positive scan cannot rule out AL when monoclonal immunoglobulin is present.[31] Increased awareness of ATTRwt as a common cardiomyopathy among the elderly, has led to increased use of bone scintigraphy, which has resulted in diagnosis of "ATTRwt" without the appropriate evaluation for the presence of monoclonal immunoglobulin. Therefore, the importance of amyloid typing cannot be emphasized enough (Figs. 3 and 4).

## Prognostication

Despite being a hematological disease, cardiac biomarkers (N-terminal pro-brain natriuretic peptide [NT-proBNP] and cardiac troponin [cTn]) formulate the most widely used prognostic system for AL amyloidosis, which divides patients into 3 major stages.[32,33] Advanced-stage cardiac disease at diagnosis is associated with a very poor survival (median ~6 months).[33] The difference between the involved and uninvolved FLC (dFLC) and clonal disease burden also showed prognostic value independent of cardiac stage.[34,35] Three models have been validated so far, but there is no clear indication under which circumstances each model performs better (Table 1). Renal impairment and atrial arrhythmias are 2 major confounders as they contribute to both NTproBNP and cTn elevation.[36] The Mayo 2004 model seems to perform better and retains its applicability in the presence of these factors compared to the other models.[36] With the addition of stage 3B (ie, those with stage 3 disease and NTproBNP ≥8500 pg/ml) it distinguishes an ultra-

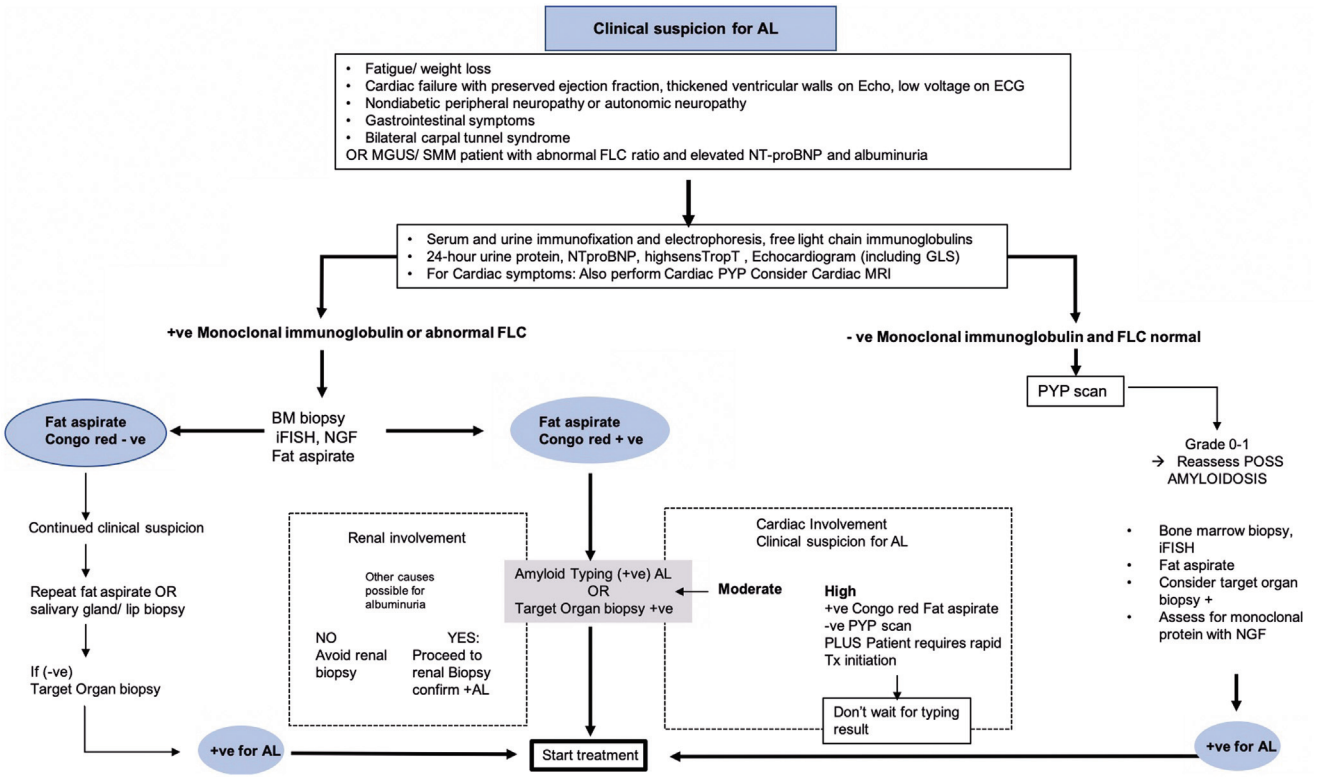


**Figure 2. Diagnostic algorithm for patient with suspected AL amyloidosis**. BM = bone marrow, Echo = echocardiogram, ECG = electrocardiogram, FLC = free light chain, GLS = global longitudinal strain, iFISH = fluorescence in situ hybridization, MGUS = monoclonal gammopathy of undetermined significance, MRI = magnetic resonance imaging, NGF = next generation flow, NTpBNP = pro-brain natriuretic peptide, SMM = Smoldering multiple myeloma, PYP scan = $^{99m}$Tc-labeled pyrophosphate scan, TropT = troponinT, Tx = treatment. The first step is to assess for the presence of monoclonal immunoglobulin by serum and urine electrophoresis, immunofixation (IFE), and serum-free light chain assay (sFLC).

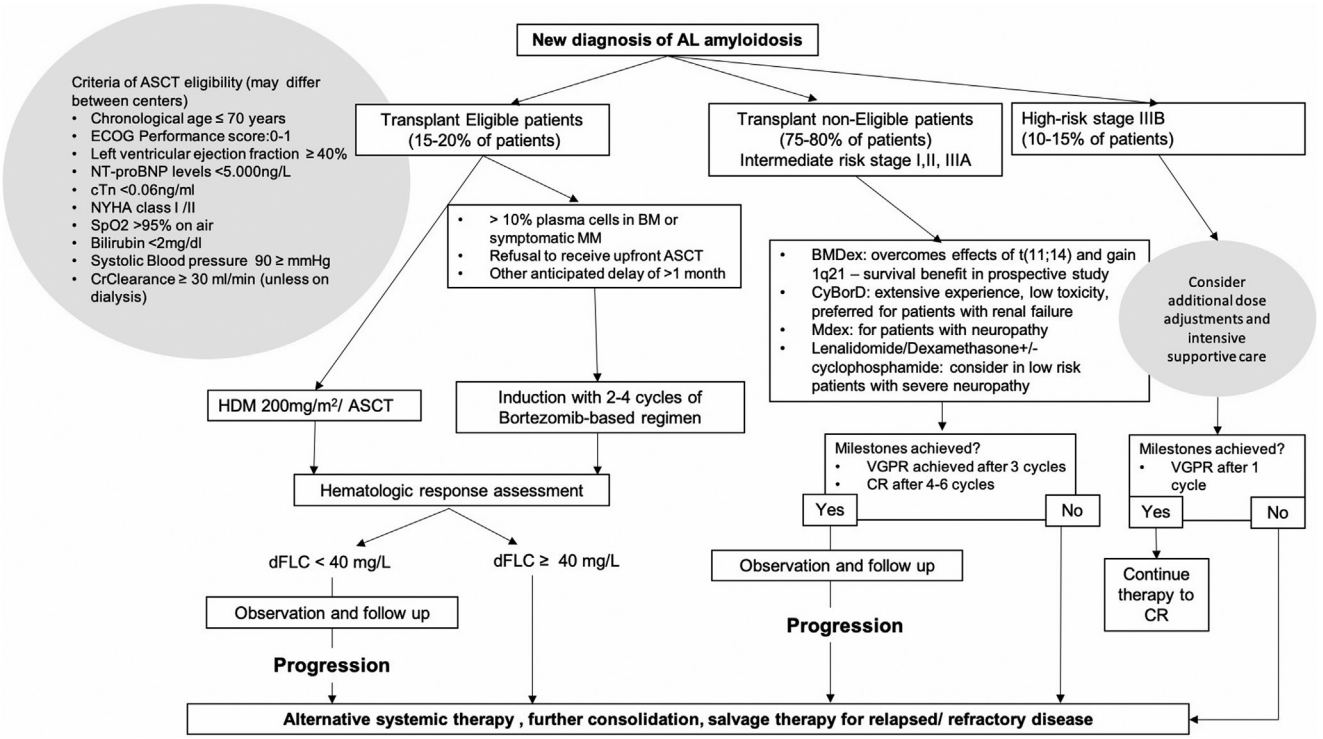


**Figure 3. Management algorithm for the newly diagnosed AL amyloidosis patient**. ASCT = autologous stem cell transplant, BM = bone marrow, BMDex = bortezomib, melphalan, dexamethasone, CR = complete response, Cr = creatinine, cTn = cardiac troponin, CyBorD = cyclophosphamide, Bortezomib, dexamethasone, dFLC = difference in involved and uninvolved free light chain, ECOG = Eastern Cooperative Oncology Group, HDM = high dose melphalan, MDex = melphalan, dexamethasone, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York heart association, SpOS = oxygen saturation, VGPR = very good partial response.

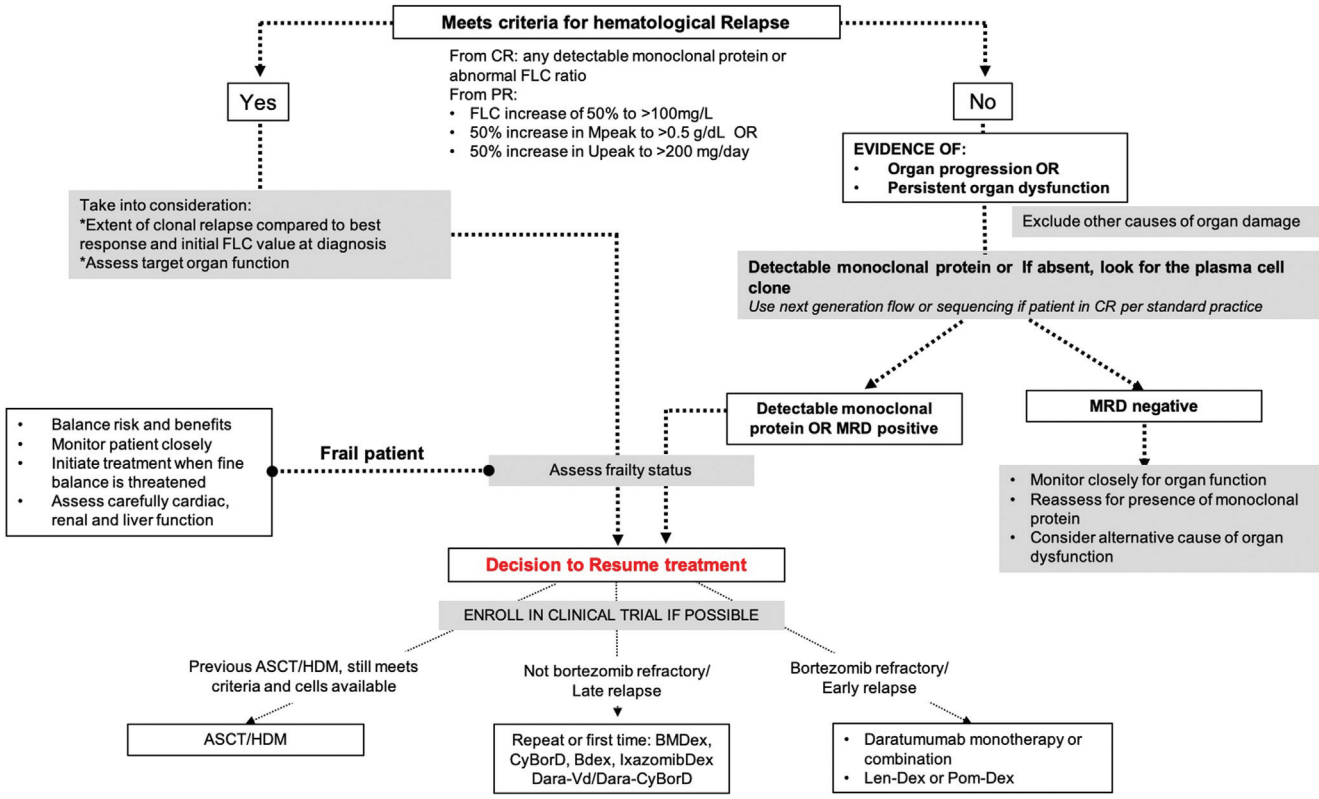


**Figure 4. Algorithm for the management of AL amyloidosis at relapse**. BDex = bortezomib dexamethasone, BMDex = bortezomib, melphalan, dexamethasone, CR = complete response, CyBorD = cyclophosphamide, Bortezomib, dexamethasone, FLC = free light chain, HDM/ASCT = high dose melphalan autologous stem cell transplant, Len-Dex = lenalidomide dexamethasone, MRD = minimal residual disease, Mpeak = monoclonal serum protein, Pom-Dex = pomalidomide dexamethasone, Upeak = monoclonal urine protein.

high risk group, with 1-year survival rate <40%. In many centers, BNP is used instead of NTproBNP; other centers use cTnI instead of cTnT while there are different generations of sensitive assays for cTnT or cTnI. The Boston University group has developed a model that uses BNP and troponin I, validated for concordance with the Mayo model[37] and the Mayo group published corresponding cutoffs for different troponin assays, NTproBNP and BNP for the 2014 Mayo stage system.[38,39]

A staging system for patients with renal involvement (also validated externally) focusing on renal outcome (progression to ESRD requiring dialysis) has also been developed, based on levels of eGFR and proteinuria.[20,40] Age, performance status, number of involved organs, and low systolic blood pressure also have prognostic significance.[33]

New biomarkers could add to the current prognostic tools. Growth differentiation factor-15 has value as a predictor of progression to end-stage renal disease and dialysis but is also associated with survival independently of other cardiobiomarkers. High levels of von Willebrand factor were linked to early death, even among patients at stage 3B.[41] Cardiac MRI may also offer prognostic information, independent of cardiac biomarkers.[42,43] Flow-mediated dilatation, a marker of vascular reactivity, which is augmented under conditions of hypotension and autonomic dysfunction was associated with early mortality and survival.[44]

**Table 1**

**Current Recommended Staging System for AL Amyloidosis and BNP Equivalent Staging System.**

| Model | Biomarkers and Cut-offs | Stages | Survival |
|---|---|---|---|
| Mayo 2004/ European | NT-proBNP 332 ng/L (or BNP 81 ng/L) cTnT 0.035 ng/mL (or cTnI 0.1ng/mL) Stage III divided based on: NT-proBNP 8500 ng/L (or BNP 700ng/L) | I: both biomarkers < cutoffs<br>II: one biomarker ≥ cutoffs<br>IIIa: both biomarkers ≥ cutoff but NTproBNP < 8500 ng/L<br>IIIb: both biomarkers ≥ cutoff but ≥ 8500 ng/L | I: no death cases<br>II: 3 years 52%<br>IIIa: 3 years 55%<br>IIIb: 3 years 19% |
| Future improved model | • *Current biomarkers NT-proBNP, cTnT, dFLC*<br>*Potential biomarkers: % clonal plasma cells in BM, indices of cardiac function using cardiac MRI, GLS in echocardiography*<br>• *Adjustment of the above for end stage renal disease* | | |

NT-proBNP = N-terminal pro-brain natriuretic peptide, BNP = pro-brain natriuretic peptide, cTnT = cardiac troponin T, cTnI = cardiac troponin I, hsTnT = high sensitivity TnT, dFLC = difference in the free light chains, BM = bone marrow, MRI = magnetic resonance imaging, GLS = global longitudinal strain.

**Table 2**

**Supportive Management in Systemic AL Amyloidosis.**

| | Symptom | Management |
|---|---|---|
| Cardiac disease | Sinus tachycardia | • Physiological and necessary to maintain cardiac output so does not need specific management in most cases (β-blockers, calcium channel blockers or angiotensin receptor blockers not tolerated well and cause bradycardia and hypotension) |
| | Cardiac failure | Diuresis:<br>• Loop diuretics are used first line<br>• Second line: spironolactone and metolazone |
| | Atrial fibrillation or flutter<br>Seen in 10% of patients with AL amyloidosis. | • Amiodarone best tolerated<br>• Digoxin should be used with care<br>• Ablation |
| | Ventricular arrythmias<br>- Common and have prognostic significance<br>- Common preterminal event is PEA | Cardiac defibrillator: Effectiveness and benefit of cardiac defibrillators is questioned with conflicting results. |
| Renal disease | Hypoalbuminemia | • Limits effectiveness of diuresis<br>• Might require albumin diuresis |
| | Nephrotic syndrome | • Angiotensin converting enzyme inhibitors are usually not well tolerated but may be considered in few, selected patients - care required with cardiac or autonomic dysfunction |
| Autonomic neuropathy | Painful neuropathy | • Gabapentin, pregabalin and duloxetine<br>• Rehabilitation and physiotherapy may also be of value |
| | Hypotension | • When no cardiac or renal involvement present: high salt diet, 40 mmHg compression stockings, fludocortisone<br>• Cardiomyopathy present: use midodrine or pyridostigmine or droxidopa |
| | Diarrhea | • loperamide as first line<br>• bile-acid binders, ocreotide and in extreme cases with parenteral nutrition. |

## Response assessment

There are 2 levels of response assessments using validated criteria: evaluation of the clonal immunoglobulin and of affected organs (Table 2). Clonal response assessment is based on serum FLCs which may be, however, below the level of reliable quantification in ~20% of patients. Currently, hematologic response criteria are validated only for serum FLCs measured by the Freelite assay[45]; new assays are available but have not been validated and FLC measurements are not interchangeable.[46,47] Reduction in the concentration of the FLC levels is the strongest predictor for prolonged survival. Even among patients with low baseline FLC levels (below "measurable" threshold), further reduction improves organ function and survival.[34,48] Timing of the hematologic response is important and early hematologic response is essential to avoid prolonged exposure of vital organs to toxic FLCs. Current criteria have been developed and validated at the 3-month landmark following therapy initiation but data from our group suggest that earlier (within the 1st month) response is critical. Even among patients in CR there may be residual clonal plasma cells producing low levels of toxic light chain, undetectable by conventional methods. Residual clonal cells are associated with a higher risk of hematologic relapse or continuous tissue toxicity. Assessment of minimal residual disease (MRD) using sensitive methods such as next generation flow (NGF) or next generation sequencing (NGS) has been incorporated in the response criteria for MM and is being introduced into clinical practice in the management of AL amyloidosis. In a recent report, patients with AL amyloidosis were assessed for MRD after one line of treatment (including post-ASCT) or at relapse and MRD was undetectable in two-thirds of patients and was associated with improved PFS and better cardiac response rates.[49] The use of high-sensitivity NGF has been explored by our group.[50] In a recent update, 45% of patients in CR were also MRD negative and none had hematologic relapse at 2 years follow-up (manuscript submitted). An emerging therapeutic goal is to tailor the treatment plan to achieve undetectable MRD using NGF or NGS (or mass spectrometry).

Organ response is a significant determinant of outcome[51,52] and criteria for the assessment of heart, kidney and liver function have been developed.[20,53] Biomarkers, such as NTproBNP or BNP for cardiac, proteinuria and eGFR for renal and ALP for liver response assessment are used. These have limitations, since biomarkers are sensitive to many un-related parameters and fluctuate significantly during therapy. NT-proBNP level is sensitive to cardiac arrhythmias, sepsis, drugs, supportive medication and renal function; proteinuria and eGFR may also change secondary to reasons unrelated to treatment response. In our experience, temporal trends rather than single measurements are more useful to assess organ function change; current organ response criteria have been based biomarker assessment on landmark timepoints. In addition, organ responses usually lag behind hematologic responses and may take months after hematologic response to reach major organ responses but simultaneous achievement of hematologic and organ responses can be seen.[52,54] Despite their limitations, significant reductions of biomarkers such as NTproBNP is associated with improved survival.[45] An effort to develop graded response criteria, in patients already in hematologic response at late landmark points[52] is under validation. Combination of biomarker-response criteria with functional tests (such as the 6-minute walking test) may be useful but lack extensive evaluation.[55] Although current organ response criteria are suboptimal, monitoring of organ function remains essential and clinical judgment should be used in combination with these evaluations.

## Treatment of AL amyloidosis

The long-term objective of treatment in AL amyloidosis is to improve organ function and prolong survival. The immediate target is to rapidly eliminate the amyloid precursor, the free light chain, through anti-clonal therapy. Chemotherapy and immunotherapy that target the aberrant plasma cells remain the mainstay of treatment. Conceptually, combinations used for MM therapy are adjusted for dose and schedule to minimize treatment-related toxicity, since patients with AL amyloidosis are more prone to treatment-related complications. In addition, some drugs (such as IMiDs) have a different toxicity profile in patients with AL amyloidosis. Treatment is tailored to individual risk stratification and response is closely monitored to adapt early in case of failure to achieve a rapid response. Despite increased efficacy and safety of new anti-clonal therapies, benefits remain significantly smaller for high-risk patients.[56] Current options include combinations of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), alkylating agents and anti-CD38 monoclonal antibodies.

Beyond administration of chemotherapy to eliminate the clone, supportive care by a multidisciplinary team is paramount to improve symptoms and treatment tolerance, but is challenging, due to multisystemic involvement and intolerance of conventional approaches. Currently, we have no proven therapies to improve reabsorption of the amyloid deposits, but despite recent negative results, immunotherapy that aims to increase amyloid deposit reabsorption is in clinical development.

## Treatments that target plasma cells

### Alkylating agents

#### High dose melphalan (HDM) with autologous stem cell transplantation (ASCT)

High dose melphalan with ASCT, yields high hematological response rates and has been used for more than 2 decades in selected patients achieving long lasting remissions and high organ response rates. However, only a minority of patients with AL amyloidosis will be eligible for HDM. Treatment-related mortality (TRM) with HDM is higher than in MM and depending on the center, the era and selection criteria may be as high as 12% to 20%.[57] Careful patient selection based on cardio-biomarkers (troponins and NTproBNP) has reduced TRM significantly.[58] The use of induction therapy is debatable, given the low tumor burden, and some centers use HDM as a single shot against the clone. Two to four induction cycles may be preferable when BM clonal plasma cells are >10% or if there is concomitant symptomatic myeloma[59] or logistics that delay HDM. Melphalan dose reductions to mitigate toxicity should be balanced against potentially lower efficacy; however, several small studies have failed to demonstrate reduced toxicity so that transplant with reduced melphalan dose is discouraged in some centers.[60] HDM with ASCT should be performed in experienced centers to reduce TRM.[57]

#### Conventional dose alkylating agents

Melphalan and cyclophosphamide (plus corticosteroids) are active against the plasma cell clone but they are currently used mostly as part of triplet combinations with novel agents. Melphalan plus dexamethasone is a safe therapy for transplant-ineligible patients with hematologic response rates up to 76%.[61] Bendamustine with dexamethasone could be an option for relapsed patients; in a recent phase II study in relapsed/refractory patients led to a 57% hematologic and 29% organ response rate but with a high (65%) rate of grade 3–4 adverse events.[62]

### Proteasome inhibitors

Targeting the proteasome has been so far the most effective therapy in AL amyloidosis. Clonal plasma cells in AL amyloidosis are particularly sensitive to PIs because they rely heavily on their proteasomes to cope with the proteotoxic stress caused by the misfolded amyloidogenic light chains.[63] Bortezomib is the first in class PI, even as single agent is very active,[64] and bortezomib-containing regimens are the standard primary therapy in most centers. Today, it is administered subcutaneously, usually once weekly, combined with dexamethasone and an alkylating agent. The most commonly used regimen is Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD), at various schedules and doses.[56,65] In the largest series, the overall hematological response rate was 60% to 65%.[56,66] CyBorD is well tolerated, does not cause significant myelosuppression, may be administered with cyclophosphamide orally or IV and is the regimen of choice for patients with renal impairment as no dose adjustments are required. However, there is data indicating that it may be less effective in patients with t(11;14) and there is no phase 3 trial to support its use.[8,10]

Oral melphalan is also combined with bortezomib and in a phase III study, bortezomib added to Melphalan + dexamethasone (MDex) achieved 81% hematological responses at 3 months compared to 57% in the MDex arm.[67] This is the only therapy that has shown a survival improvement in a randomized study. In addition, BMDex may be able to overcome the disadvantage of MDex in patients with 1q21 gain and that of bortezomib for patients with t(11;14) translocation.[8,10] Melphalan dose needs renal adjustment, while myelotoxicity may be more pronounced, including late effects such as myelodysplastic syndromes. Neuropathy is the primary toxicity of bortezomib, and its use should be avoided in patients with severe peripheral or autonomic neuropathy. A signal of cardiotoxicity may exist with bortezomib; atrial arrhythmias may be more frequent with IV administration than with SQ bortezomib.

Ixazomib is a second-generation orally administered PI which has shown single agent activity in phase I/II studies in relapsed AL amyloidosis patients and is a rescue option for these patients.[68] In the phase III TOURMALINE-AL1 study, Ixazomib-dexamethasone was compared to physician's choice regimens (not containing bortezomib), in patients with relapsed AL amyloidosis. Although ixazomib/dexamethasone was not associated with higher rates of hematologic response (53% vs 51%),[69] it was effective and safe; a CR was achieved by 26% (vs 18% in the control arm) and hematologic responses were long lasting (46.5 months vs 20.2 in physician's choice arm). Vital organ PFS was also longer (18 vs 11 months in the Ixazomib and physician's choice arm respectively). Hematologic responses were higher in bortezomib naïve vs exposed patients, but clinically relevant time to event end-points still favored ixazomib/dexamethasone.[70] Ixazomib combined with cyclophosphamide and dexamethasone is safe and well tolerated in newly diagnosed Pi naïve AL amyloidosis patients and induced ≥VGPR in 39% of patients in a phase I/II trial presented recently.[71] A retrospective series also indicated efficacy and safety for the combination of ixazomib with lenalidomide and dexamethasone in the relapsed setting.[72]

Carfilzomib is an irreversible second-generation PI with a favorable efficacy profile compared to bortezomib in MM patients with relapsed/refractory disease. However, the cardiovascular toxicity associated with carfilzomib limits its use in patients with AL amyloidosis. In a phase I/II study, in relapsed/refractory patients with AL hematological responses were observed in 63%, but 46% experienced grade 3/4 cardiovascular adverse events and renal function deterioration.[73] In a small series (N=5) carfilzomib was safe and active in patients with peripheral neuropathy.[74] The results of a dose-finding study of Carfilzomib plus dexamethasone (Kd) are awaited (NCT01789242).

### IMiDs

The response to IMiDs is usually slower than with bortezomib and their place is mostly in the relapsed setting. Thalidomide is associated with significant toxicity, low doses are used and today it is less preferred.[75] Lenalidomide, at lower than standard doses, has been combined with MDex or cyclophosphamide/dexamethasone, leading to 38%–68% and 46%–60% hematological responses, respectively, in patients previously untreated[76,77] or patients refractory to bortezomib, thalidomide, and alkylating agents. Lenalidomide-associated toxicities in patients with AL amyloidosis, include myelosuppression, skin rashes, infections, thrombotic complications and fatigue; deterioration of renal function has also been observed. Pomalidomide has a safer renal profile and perhaps better tolerability in patients with AL amyloidosis compared to lenalidomide. It can overcome lenalidomide resistance and induces rapid hematological responses in 48% to 68% of patients.[78,79] A common pattern with all IMiDs is a paradoxical increase in NT-proBNP (usually transient), which makes assessment of cardiac response challenging. The upfront combination of bortezomib and low dose lenalidomide was reported form our group, with hematology response in 89% on intent to treat, including CR in 32% and VGPR in 57%, however, 38% required dose reductions and 27% discontinued lenalidomide due to toxicity.[80] A similar combination with Pomalidomide, bortezomib and dexamethasone was associated with toxicity and early mortality.[81]

### Monoclonal antibodies

Daratumumab is an anti-CD38 monoclonal antibody, with very promising activity in patients with relapsed/refractory AL amyloidosis,[82–84] moving rapidly to the frontline setting. In heavily pretreated patients, daratumumab monotherapy was associated with high response rates (63%–100%), including CRs in up to 36%. Importantly these occur rapidly (usually within the first month). It has been administered also in combination with bortezomib or IMiDs, as in MM.[85] A phase III study is currently comparing daratumumab (as a subcutaneous injection) plus CyBorD vs CyBordD in the upfront setting (NCT03201965). In the safety run-in of the study, 96% of patients responded in the D-CyBorD and 82% achieved at least VGPR.[86] Another ongoing trial is assessing the safety and efficacy of Daratumumab monotherapy in previously untreated AL amyloidosis patients with ultra-high risk (stage 3B) disease (NCT04131309). Elotuzumab (an anti-SLAMF7 monoclonal antibody) added to IMiDs (lenalidomide) may be safe in patients with relapsed AL amyloidosis, but further investigation is needed.[87]

## Treatment strategy

The treatment of a patient with AL amyloidosis should be individualized based on risk assessments and should be response-adapted at all stages. Patients are stratified according to standard risk models (we use Mayo 2004 model modified with the addition of stage 3B). Beyond cardiac status, which is the critical component of prognosis, renal and liver function should be evaluated, peripheral and autonomic neuropathy, nutritional status and other co-morbidities. The target is to achieve a complete hematologic response or, at least very low levels of serum FLCs, as soon as possible, with limited toxicity. At all stages of treatment, major emphasis is given on supportive management which requires expert input from multiple specialties including cardiologists and nephrologists. Adverse event management and prevention and appropriate organ function support are key to treatment success (Table 3). Patients should be monitored closely for cardiac complications and peripheral neuropathy, and should be educated to adjust fluid intake and diuretics, have regular contact with treating physicians.

Patients who may be ASCT-eligible are usually younger than 65 to 70 years, mostly with stage 1–2 disease; NTproBNP and troponin thresholds differ in each center. We use induction therapy before HDM/AST; some patients may become eligible post-induction but in others organ function deterioration may not allow transplant.[88] Deferred transplant may also be an option for some pateints.[89] Post-ASCT, consolidation can be considered when optimal response has not been achieved.[90] Our strategy is to start with bortezomib-based, stem-cell sparing regimens and assess hematologic response and organ function frequently. For patients in hematologic CR after 4 to 6 cycles, we assess MRD status using sensitive NGF and ASCT/HDM might be offered as option for consolidation therapy in patients who have detectable MRD. For patients in PR or VGPR after induction, ASCT/HDM is discussed weighing transplant toxicity vs efficacy and availability of other options.

For patients not eligible for HDM, CyBorD is our preferred regimen, administered weekly, with SC bortezomib and intravenous or oral cyclophosphamide at 500 mg flat dose, with dexamethasone weekly at 10 to 40 mg. Hematologic response is evaluated monthly and treatment modification is considered if the response following 3 cycles of treatment is less than a VGPR; usually to include an IMiD (instead of cyclophosphamide) or daratumumab. For patients with at least VGPR after 3 cycles we plan for a total of 6 to 8 treatment cycles aiming for CR. If CR is achieved, MRD status using NGF is also assessed. In patients with less than CR and no organ response we discuss additional therapy, either with the same regimen (if in VGPR) or preferably with a modified treatment. For MRD negative patients the probability of relapse is very low, and we follow without further therapy. Following treatment completion all patients are monitored regularly for hematological relapse and vital organ function, preferably with biomarkers.

For stage 3B patients, anti-clonal therapy alone may not be enough even when hematologic response is achieved rapidly. Early mortality may be as high as 50% following therapy initiation.[33] Close collaboration with the heart failure clinic is required, and cardiac transplantation should be discussed for younger patients. Immediate treatment initiation is crucial. Standard bortezomib doses may be toxic, lower doses (1 or 0.7 $mg/m^2$) plus dexamethasone at low doses may be better tolerated. Close monitoring is advised; inpatient treatment administration and cardiac monitoring may be considered. Switching to an

**Table 3**

**Hematological and Organ Response Criteria.**

| | Response | Definition |
|---|---|---|
| Hematological | CR | Normalization of FLC levels and ratio<br>Negative urine and serum IFx |
| | VGPR | Reduction in dFLC to < 40mgl/L |
| | Partial response (PR) | Greater than 50% reduction in dFLC |
| | No response | Less than PR |
| | Progression | From CR: any detectable monoclonal protein or abnormal FLC ratio<br>From PR:<br>FLC increase of 50% to >100mg/L<br>50% increase in Mpeak to >0.5 g/dL OR<br>50% increase in Upeak to >200 mg/day |
| Cardiac | Response | NT-proBNP >30% and >300ng/L decrease OR<br>≥ 2 classes of NYHA decrease (in patients with baseline NYHA 3 or 4) |
| | Progression | NT-proBNP >30% and >300ng/L increase OR cTn ≥ 33% increase or ejection fraction progression (≥10% decrease) |
| Renal | Response | 50% decrease (≥ 0.5 g/day) of 24-hour urine protein (with pre-treatment urine protein >0.5 g/day)<br>*Creatinine and creatinine clearance must not worsen by 25% over baseline.* |
| | Progression | 50% increase (≥ 1 g/day) of 24-hour urine protein to >1 g/day or 25% worsening of serum creatinine or creatinine clearance |
| Liver | Response | 50% decrease in ALP<br>Liver size decrease radiographically by ≥ 2 cm. |
| | Progression | 50% ALP increase > the lowest value |
| Peripheral nervous system | Response | Improvement in EMG nerve conduction velocity |
| | Progression | Progressive neuropathy by EMG nerve conduction velocity |

ALP = alkaline phosphatase, CR = complete response, dFLC = difference between the involved and uninvolved FLC, EMG = electromyogram, FLC = free light chain, IFx = immunofixation, Mpeak = monoclonal serum protein, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart association, PR = Partial response, Upeak = monoclonal urinary protein, VGPR = Very good partial response.

alternate regimen (adjusted for cardiac risk) may be considered for non-responders as early as 1 month following treatment initiation. Addition of IMiDs may be challenging; daratumumab may be the preferred option, but there is limited experience in stage 3B patients.

## Management of relapse

Disease relapse will occur in many patients while a significant proportion will not achieve sufficiently deep hematologic response with first line therapy and will require second-line treatment. Criteria to define hematologic relapse require significant increase in the level of FLCs. For many patients it may, however, be detrimental to wait for a substantial FLC increase before starting salvage therapy. In most cases, hematological relapse precedes organ progression, and should be used as a sensitive indicator for treatment initiation. However, there is no clear consensus on which timepoint and under what conditions second-line treatment should be started.[91,92] Multiple factors need to be taken into consideration, including magnitude of FLC increase, pattern of organ involvement and degree of dysfunction, depth of hematological response to prior lines. Some patients will present with organ function deterioration or persistent organ dysfunction without an FLC increase; the decision to start treatment will also depend on whether monoclonal immunoglobulin can be detected: if no monoclonal immunoglobulin is detected but there is persistent MRD, treatment may be considered. Treatment should preferably start earlier than later, especially in patients with cardiac involvement. In cases of clonal disease persistence or reappearance and stable organ function, the therapeutic approach can be less aggressive. For patients with end-stage organ function (dialyzed patients), one might opt for close monitoring to avoid treatment-related toxicity.[91,92] Bortezomib-based combinations can be considered following ASCT at relapse or as re-treatment in late relapses (12–18 months post last bortezomib dose). A second HDM/ASCT could also be an option if the patient maintains eligibility but experience is limited. IMiDs may be used either alone (with dexamethasone), with cyclophosphamide or added to bortezomib backbone. Daratumumab-based therapy is probably the most attractive option in this setting with supportive data from retrospective[83] and prospective studies.[83,84] There is ongoing data collection on the use of venetoclax in patients with t(11;14); this drug has shown single agent activity in small case series/reports but prospective data are lacking in patients with AL.[93]

## Targeting amyloid deposits

Three antibodies that target amyloid deposits directly have been developed to date: NEOD001, anti-SAP antibody (dezamizumab), and 11–1F4. Initial optimism derived from phase I/II clinical trials, was not confirmed in randomized phase II/III trials, and clinical development of NEOD001 and dezamizumab have stopped[94,95]; a post-hoc analysis though suggested some potential benefit in high risk patients. 11-1F4 is the only amyloid-directed antibody still in development. In an open-label phase I trial a total of 27 patients with relapsed/refractory AL amyloidosis were treated and organ response was seen in 61% of evaluable patients. A phase III clinical trial is expected to start this year.[96] The role of amyloid-directed immunotherapy in the treatment of AL amyloidosis needs to be carefully revisited and planned with future trials.

## The role of organ transplantation

Transplantation of a major affected organ is an important strategy to manage the disease in selected patients. Heart transplantation outcomes have improved substantially in the past

years, but are still used in a very small number of highly selected patients. Kidney transplantation is used more extensively, and organ survival may be similar to that of other diseases.[97–99] A key improvement has been our ability to achieve and maintain complete hematologic responses protecting the transplanted organs from amyloid recurrence. However, organ transplantation is still under-used in AL amyloidosis. Key issues remain availability of organs and optimal transplant timing: should we wait for deep hematologic response or can we do the transplantation before we achieve this goal.

## Conclusions

Insight and understanding of the processes that underly amyloidogenesis remain poor and are perhaps the key to a future, more successful management of this unique disease. It is expected that the use of novel immunotherapies that target the plasma cell clone may further improve hematologic response rates and outcomes but we are still far from the development of effective amyloid-targeting therapies. However, key to successful management and improvement of patients' outcomes remains the early recognition and diagnosis of the disease. This requires the education of physicians of many different disciplines and perhaps the potential use of screening strategies in high risk individuals with the use of biomarkers.

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