Diagnosis and treatment of AL Amyloidosis in 2015: Consensus guidelines of the Belgian Hematological Society

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Immunoglobulin light chain amyloidosis is a clonal plasma cell dyscrasia, historically associated with a very poor prognosis. Prompt diagnosis is critical to preserve organ function and improve survival in immunoglobulin light chain amyloidosis patients. The severity of cardiac involvement and response to treatment are the most important prognostic factors. Serum free light chain ratio and cardiac biomarkers troponin T and N-terminal pro-brain natriuretic peptide are powerful tools for the evaluation of prognosis and treatment response. Historically, treatment with autologous stem cell transplantation appears to offer a survival benefit, but is only an option in a minority of patients. IMiDs, and especially proteasome inhibitors, have shown promising activity in immunoglobulin light chain amyloidosis. Supportive care should be integrated in the treatment plan and requires a multidisciplinary approach. These guidelines summarise a consensus of the myeloma subcommittee of the Belgian Hematological Society on diagnosis, cytoreductive and supportive treatment of immunoglobulin light chain amyloidosis, based on an extended review of the literature. Where applicable, comments were added with respect to the Belgian reimbursement modalities.
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Introduction

Organ damage in immunoglobulin light chain amyloidosis (AL) is caused by the deposition of misfolded clonal immunoglobulin light chains as pleated sheets. As opposed to other plasma cell disorders, a dominancy of lambda light chains (1:3 κ:λ) is found in AL. Untreated, this process inevitably leads to progressive organ failure and death. Incidence of AL is 1:100.000 and mean age at diagnosis is 63 years. Other types of systemic amyloidosis (hereditary, senile and secondary) are important to distinguish from AL, because these require a different treatment. Localised amyloidosis is a different entity, presenting in the skin, larynx, brain, bladder or as solitary pulmonary nodules and can be treated conservatively or with laser therapy.[1]

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Table 1. Criteria for the diagnosis of AL amyloidosis.[4]

All four criteria must be met:
Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract or peripheral nerve involvement).
Positive amyloid staining by Congo red in any tissue (e.g. fat aspirate, bone marrow or organ biopsy).
Evidence that amyloid is light chain-related established by direct examination of the amyloid (immunohistochemical staining, direct sequencing, etc.).
Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal free light chain ratio or clonal plasma cells in the bone marrow).
NB: Approximately 2-3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed above; the diagnosis of AL amyloidosis must be made with caution in these patients.

Clinical presentation

A high index of suspicion is required by all physicians, since all organs, except for the central nervous system, can be affected. Symptoms are nonspecific, often resulting in a diagnostic delay, which has a negative impact on prognosis. Organ involvement is defined by consensus criteria.[2,3] A biopsy is required to confirm a clinical suspicion of amyloidosis. Kidney involvement is most frequent (60% at diagnosis), sometimes presenting with nephrotic syndrome. If a kidney biopsy is not available, >0.5 grams/day albuminuria together with a positive biopsy in another organ, will lead to diagnosis. Up to 50% of patients present with diastolic heart failure at diagnosis and cardiac involvement accounts for 75% of deaths. Voltage loss on ECG is an early hallmark of cardiac amyloidosis and poor R-wave progression in the chest (pseudoinfarction pattern) occurs in up to 50% of patients with cardiac AL amyloidosis. Concentric hypertrophy of the ventricular wall and thickening of the interventricular septum can be seen on echocardiography. Liver enlargement is present in 30%, usually associated with a rise in serum alkaline phosphatases. Autonomic (orthostatism) or peripheral sensorimotor neuropathy is present in up to 20% of patients. Gastrointestinal (GI) tract involvement is commonly found by rectal or gastric biopsies and can be associated with GI bleeding, malabsorption, perforation, diarrhoea and obstruction. Macroglossia (14%) or periorbital ecchymoses ('raccoon eye') (11%) are rare, but pathognomonic for AL, as is the 'shoulder pad sign' (15%), caused by periarticular amyloid infiltration. Factor X absorption of amyloid deposits and capillary fragility increase the risk of bleeding.

Diagnosis

Criteria for the diagnosis of AL amyloidosis are listed in *Table 1*.[4]

AL amyloidosis should be considered in case of nephrotic range proteinuria, non-ischemic cardiomyopathy, peripheral demyelinating polyneuropathy with a monoclonal component, autonomic neuropathy with weight loss and unexplained hepatomegaly or increased alkaline phosphatases without imaging abnormalities of the liver.

The diagnosis is made on a biopsy of an involved organ. Bone marrow biopsy has a sensitivity of 60% and the median plasma cell percentage is low (7%). If amyloidosis is suspected on clinical grounds, fine needle aspiration of abdominal fat is the preferred diagnostic test, as it is non-invasive, inexpensive, and has a high sensitivity (88%) and specificity (97%).[3] An instructive video can be found on www.amyloid.nl. Amyloid deposition is demonstrated by Congo red staining or electron microscopy. Immunohistochemical staining is frequently unreliable to discriminate between AL, hereditary, secondary or senile amyloidosis and the mere presence of a monoclonal protein could be a coincidental monoclonal gammopathy of unknown significance (MGUS), as this is a common finding. Therefore, tissue biopsy laser micro-dissection with mass spectrometry, offered only at specialised centres abroad, is now considered the gold standard for amyloid typing.[5] Reference centres are the Royal Free Hospital, UK and the University di Pavia Hospital, Italy.

Required tests at diagnosis are: protein electrophoresis and immunofixation; IgG, IgA and IgM quantification; sFLC assay; serum beta-2-microglobulin; serum crea-

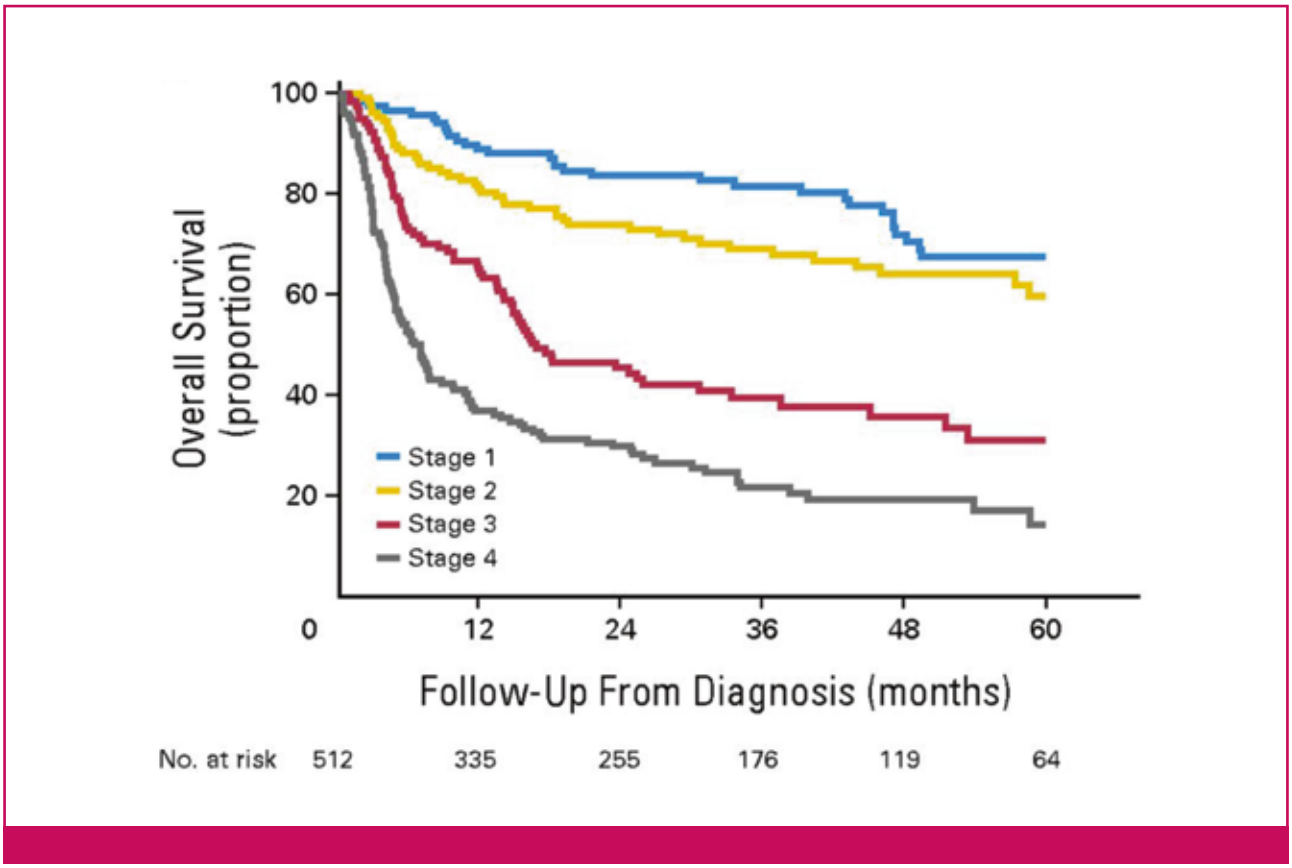

Figure 1. Kaplan-Meier curves for overall survival (OS) from diagnosis among 758 patients based on the new staging system. A score of 1 is given for each of three prognostic variables (cTnT ≥ 0.025 ng/mL, NT-ProBNP ≥ 1,800 pg/mL, and dFLC ≥ 18 mg/dL), leading to four stages (I, II, III, and IV) with scores of 0, 1, 2, and 3, respectively. The median OS from diagnosis for stages I, II, III, and IV disease was 94.1 months (95% CI, 64 to 154), 40.3 months (95% CI, 24 to 59), 14.0 months (95% CI, 11 to 18), and 5.8 months (95% CI, 5 to 7), respectively (P < .001). The 5-year survival estimates for patients with stages I, II, III, and IV disease were 59%, 42%, 20%, and 14%, respectively.[10]

tinine, calcium, alkaline phosphatases; 24h urine protein electrophoresis (UPEP) with immunofixation and creatinine clearance; cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP). Additional workup includes bone marrow biopsy with FISH to detect translocations t(4;14), t(14;16), t(11;14) and deletion 17p within plasma cells, however this is often unsuccessful due to low plasma cell counts.
To rule out multiple myeloma (MM), skeletal X-rays or low voltage total body CT scans are performed. In case of high suspicion and normal radiology, spinal MRI is recommended because of its high sensitivity. Directed organ screening based on clinical guidance is indicated to establish the extent of the disease. When cardiac amyloidosis is suspected, ECG and Holter monitoring are considered for diagnosis of arrhythmia, and echocardiography and cardiac MRI for evaluation of ventricular septum thickness and cardiac function. Cardiac biomarkers troponin T and NT-proBNP are markers for cardiac damage in AL. In the presence of renal failure, they provide a composite view on both organ systems. Abdominal ultrasound can be useful to investigate the liver and spleen, and upper and lower endoscopy may be required in case of GI bleeding, uncontrollable diarrhoea or significant weight loss. Iodinated serum amyloid P scintigraphy (SAP-scan) is a diagnostic tool for imaging organ distribution at diagnosis or follow-up, with exception of cardiac involvement.[6] It was developed in London, UK and is also available in Groningen, NL but not in Belgium. The BHS myeloma subcommittee does not recommend the routine use of SAP scans outside clinical trials.

Patients with MGUS and an abnormal serum FLC are at higher risk of developing amyloidosis. They should have life-long monitoring for symptomatic MM and regular assessment of NT-proBNP and urine albumin to trigger additional investigations for amyloidosis.[7]

Table 2. Criteria for hematologic response in AL amyloidosis.[2]

Complete response (CR)	Serum and urine negative for a monoclonal protein by means of immunofixation, normal kappa/lambda FLC ratio, and normal absolute value of the involved serum FLC (in patients without renal failure).
Partial response (PR)	Serum M-component > 0.5 g/dl and 50% reduction; light chain in the urine with a peak > 100 mg/day and 50% reduction; or FLC > 10 mg/dl and 50% reduction.
Progression after CR	Any detectable M-protein or abnormal FLC ratio (light chain must double).
Progression after PR or stable disease	50% increase in serum monoclonal protein to > 0.5 g/dl or 50% increase in urinary monoclonal protein to > 200 mg/day with a visible peak. FLC increase of 50% to 10 mg/dL.

Response monitoring and prognosis

Prognosis in amyloidosis depends on host factors (e.g. age, performance status, co-morbidities), the extension and severity of organ involvement and hematologic response to therapy.[8] Hematologic response is monitored by a decrease in the dFLC, the difference between involved and uninvolved light chains. Normalisation of the serum FLC ratio in response to therapy is a strong predictor of survival.

Cardiac involvement, present in nearly half of the patients, has the greatest impact on survival. Elevated serum cardiac troponin T and NT-proBNP are sensitive and reproducible prognostic markers in AL amyloidosis. The Mayo cardiac staging system distinguishes between three stages. In stage I, levels of troponin T and NT-proBNP are normal, in stage II there is an increase in one marker and in stage III, both markers are elevated, with thresholds at 332 pg/ml for NT-proBNP and at 0.035 μg/L for troponin T.[9] A reduction of 30% of NT-pro-BNP qualifies as response and normalisation correlates with improved survival.

A revised prognostic staging system, validated at diagnosis and during treatment, using the combination of dFLC and cardiac biomarkers troponin T and NT-proBNP, divides AL patients into four groups with major differences in overall survival (OS): 94.1 months for stage I and 40.3, 14, and 5.8 months, for stages II, III, and IV, respectively (*Figure 1*).[10]

Organ response according to Gertz et al. can be evaluated in the heart by a decrease in the mean interventricular septum thickness by 2 mm, 20% improvement in ejection fraction, improvement by 2 NYHA classes (without an increase in diuretic use and no increase of wall thickness) or a reduction (≥30% and ≥300ng/l) of NT-proBNP, often seen early after treatment initiation, but only in patients with an eGFR ≥ 45ml/min/1.73m^2.

Organ response in the kidney is defined by a 50% decrease (at least 0.5g/day) in 24h urinary protein with a stable creatinine clearance (≤25% decrease over baseline level), and in the liver by a 50% decrease in abnormal alkaline phosphatases or at least 2 cm decrease in liver size on radiographic imaging. Neurological response is rare and defined by an improvement in nerve conduction velocity on electromyogram.[2]

Differential diagnosis

Systemic AL should be distinguished from other forms of amyloidosis. In these cases, the presence of a serum or urine monoclonal protein leads to misdiagnosis in 10%, as MGUS is not uncommon in patients with other types of amyloidosis.[11]

In AA amyloidosis there is a deposit of serum amyloid A protein (SAA) due to chronic inflammation or infectious diseases. Senile amyloidosis classically occurs in older men with isolated cardiac involvement and treatment is supportive. In hereditary amyloidosis, a mutation in the gene encoding a protein precursor (i.e. lysozyme, apolipoprotein A1, apolipoprotein A2, fibrinogen, gelsolin and transthyretin) results in increased amyloidogenicity. Transmission is autosomal dominant but familial history may be absent due to incomplete penetrance and variable presentation. Diagnosis should be considered in the absence of staining with an anti-light chain antibody, using mass spectrometry-based proteomic analysis. Molecular analysis of hereditary mutations in amyloid proteins and direct amyloid fibril sequencing can be performed at specialised centres. Hereditary TTR-related (ATTR) amyloidosis is particularly common in African-Americans (3%) and requires liver transplantation. Another differential diagnosis is Randall-type LC deposit disease (LCDD).[12] Presenting symptoms include proteinuria, nephrotic syndrome and

Table 3. Risk categories for ASCT in AL amyloidosis.[29]

Low risk	Any age, 1-2 organ(s) involvement, no cardiac involvement and creatinine clearance >50 ml/min.
Intermediate risk	>71 year-old, 1-2 organ(s) involvement, one of which may be cardiac or renal, with creatinine <51 ml/min.
High risk	Three organs involvement or advanced cardiac involvement.

impaired renal function. MM is present in 30-60% of cases and a monoclonal Ig is detected in the serum and/or urine in up to 90% of patients. In addition, haematuria and hypertension are commonly observed, whereas extra-renal manifestations are rarely present at diagnosis. Diagnosis is made on kidney biopsy using immunofluorescence (kappa isotype being 2-3 times more frequent than lambda isotype) or electron microscopy.

Treatment

The goal of treatment is rapid reduction of the culprit plasma cell clone in order to rescue organ function. There is a clear relationship between hematologic response, organ response and survival. Survival improves in the presence of hematologic response after three months of therapy. Quality of response is important and a CR, defined as a normal FLC ratio or a VGPR, defined as dFLC <40 mg/L is the goal of treatment.[13]

Autologous stem cell transplantation

More than 50 nonrandomised trials have confirmed the efficacy of high dose melphalan followed by autologous stem cell transplantation (ASCT), with organ response rates up to 65% in a proportion of eligible patients.[14] However, the only randomised trial comparing ASCT with Melphalan-Dexamethasone failed to identify any difference in terms of OS or PFS and was especially hindered by lack of randomisation for cardiac involvement and a very high transplant related mortality.[15] This treatment option should ideally be performed in the setting of a clinical trial. Eligible patients are under 65y, have less than three organs involved and have a good cardiac condition, as measured by troponin T and NT-proBNP levels. The mentioned Mayo amyloidosis staging system separates patients into three groups with very significant differences in OS, but cut-offs are too stringent to exclude patients from transplantation. Based on a retrospective analysis, Gertz et al. only exclude patients with troponin T >0.06 μg/L and NT-proBNP >5000 pg/ml.[16] In frail patients, mortality risk is reduced by attenuating the melphalan conditioning dose (100-140 mg/m^2) at the price of lower response and survival rates.[17] Current data on tandem ASCT in AL are scarce and the increase in toxicity does not result in a significant therapeutic benefit. Allotransplantation in AL is limited to anecdotal reports and is hampered by a high treatment related mortality (TRM).[18]

Peripheral blood stem cell (PBSC) mobilisation in AL patients is hazardous and can be associated with volume overload, arrhythmia, capillary leak syndrome or even sudden cardiac death. To minimise the risk of toxicity, G-CSF alone (5 μg/kg every 12h for five days) is recommended for mobilisation.[19] Plerixafor in AL patients has not been studied in a well-designed clinical trial.

Conventional chemotherapy

The current gold standard treatment for AL is melphalan 10 mg/m^2/day, days 1-4, plus high-dose oral dexamethasone 40 mg/day, days 1-4 (M-Dex), every 28 days until stable remission with a maximum of twelve months.[20]

Novel agents-based regimens

Newer myeloma treatments challenge the gold standard regimen. In contrast with MM, these agents are not reimbursed for AL in Belgium. Some patients have concomitant MM for which these agents are registered and in most AL trials, novel agents are implemented.

Bortezomib as a single agent, induces rapid hematologic responses in 50% of patients, with 20% CR.[21] The combination of bortezomib, cyclophosphamide, and dexamethasone (VCD) has been explored in two retrospective analyses reporting unprecedented results, with 81.4-94% hematologic responses and a 39.5-71% CR. The reversal of poor outcome in patients with cardiac involvement is the main achievement of this regimen. It was administered for two to eight cycles of weekly or biweekly bortezomib 1.3 mg/m^2, cyclophosphamide 300 to 700 mg orally weekly and dexamethasone 40 mg once or twice a week, and followed by ASCT in eligible

patients.[1,22,23] In advanced cardiac disease, bortezomib should be used with caution as it may induce abrupt reduction in left ventricular ejection fraction. A weekly subcutaneous (SC) administration of bortezomib is preferred in the AL setting. Even in patients with high risk cardiac AL, the VCD regimen can achieve a high number of hematologic and cardiac responses.[24] However, the addition of bortezomib to the M-Dex backbone seems to benefit mainly patients without severe heart failure (NT-proBNP <8500 ng/l) and those who are not fit enough to receive high-dose Dex. Patients who can receive high dose Dex in combination with melphalan had similar response rates and survival with or without bortezomib in a retrospective analysis.[25]

Patient stratification to tailor treatment according to disease status is a matter of debate at the current juncture of older and newer therapies. Transplant eligible low risk patients (NT-proBNP <5000 ng/L) can be treated with an upfront ASCT.[7] Alternatively, the VCD regimen can be used as a transplant sparing regimen, reserving ASCT for patients not in CR or with an early relapse. In intermediate risk patients (NT-proBNP between 5000 and 8500 ng/L), M-Dex is an effective and well tolerated option, followed by ASCT in selected patients.[26] Due to the higher short term efficacy and tolerability compared to M-Dex, there is a trend to treat these patients with VCD, but long-term results are lacking. In very high risk AL patients (NT-proBNP >8500), a reduced VCD regimen with weekly bortezomib (1 mg/m^2) and dexamethasone (10-20 mg) is feasible with a gradual and cautious dose increase.

Immunomodulating analogues of thalidomide, the IMiDs, are under investigation in AL. Thalidomide is poorly tolerated, but lenalidomide at a reduced dose of 15 mg daily, combined with cyclophosphamide and dexamethasone produces a 60% response rate and is well tolerated, with the convenience of an oral regimen and without the risk of neuropathy associated with bortezomib-based treatments.[27,28] With lenalidomide, renal toxicity and NT-proBNP rises are of concern. Whether the latter is indicative of cardiac toxicity or whether NT-proBNP is not a reliable marker of cardiac function in IMiD-treated AL patients is unknown.[29]

Anecdotal reports with second generation proteasome inhibitors and pomalidomide show promising response rates in heavily pretreated patients, but these data need to be confirmed in larger multi-centre trials.

Current therapies are aimed at targeting malignant plasma cells, but not the amyloid deposits causing organ damage. New therapeutic approaches, targeting light chain fibril compounds, will hopefully be used in combination with existing therapies to achieve a cure for AL. A global phase III clinical trial with a monoclonal antibody against misfolded proteins (NEOD001) is recruiting for patients with cardiac amyloidosis (clinicaltrials.gov identifier NCT02312206 VITAL study).

Supportive organ care

Organ function starts to improve several months after the achievement of a hematologic CR and often continues to improve over time. Meanwhile, supportive measures remain critical in the management of AL amyloidosis.

For patients with cardiac amyloidosis and fluid overload, loop diuretics are the mainstay of treatment. Digoxin is contra-indicated for atrial fibrillation, as it seems to bind to amyloid deposits, with increased toxicity. Amiodarone is preferred as first-line therapy for arrhythmia. Pacemaker or defibrillator implantation is sometimes required. Angiotensin converting enzyme (ACE) inhibitors can be considered to reduce proteinuria, but caution is warranted in case of poor cardiac output or hypotension. Calcium channel blockers can aggravate congestive heart failure and beta-blockers have shown to increase mortality in cardiac AL. Fludrocortisone for postural hypotension is often poorly tolerated as it may increase fluid retention.[30] Renal amyloidosis is treated with ACE inhibitors in case of hypertension and diuretics in case of nephrotic syndrome. For end-organ renal disease, haemodialysis and peritoneal dialysis are associated with a similar survival. For gastroparesis, prokinetic agents can be used and for diarrhoea, loperamide and octreotide are effective.

Solid organ transplantation

The systemic nature of AL and the possible recurrence in the graft render this treatment option contentious. Renal transplantation can be considered after ASCT and results in prolonged survival in patients with no extrarenal amyloid deposition.[31] A median graft survival of 8.9 years can be expected. Heart transplantation has been carried out before and after ASCT with acceptable outcomes in small series. Cardiac transplantation can be considered in patients with isolated end-stage cardiac failure who would otherwise be eligible for ASCT. In this setting, transplantation should be followed by chemotherapy in order to prevent recurrence of cardiac amyloid or deposition in other organs. Liver transplantation has been performed in a very small number of cases with disappointing results.[32]

Key messages for clinical practice

1. Early diagnosis of AL is crucial to avoid end-organ damage. In that regard, patients with MGUS and an abnormal sFLC ratio should undergo yearly measurement of proteinuria and NT-proBNP levels.
2. Prognosis and response to therapy are evaluated using the differential sFLC ratio and cardiac biomarkers Troponin T and NT-proBNP.
3. The VCD regimen is a potential new standard for the first-line treatment of a large number of AL patients and reimbursement by the Belgian authorities is urgently needed. When possible, inclusion in prospective clinical trials with novel agents is recommended. The role of ASCT needs to be redefined in the era of bortezomib induction, especially in patients having achieved a complete remission.

Conclusion

AL is a rare disease and diagnosis and treatment should be coordinated by experts. When available, treatment in clinical trials is highly recommended. Cardiac involvement and hematologic response to treatment are the most important prognostic factors in AL. Serum (d) FLC and cardiac biomarkers troponin T and NT-proBNP are the tools for monitoring prognosis and response to therapy. Based upon the depth and the promptness of responses, combined with a low morbidity and mortality, VCD is a potential future standard of care for patients with newly diagnosed AL, to be prospectively validated in randomised clinical trials. Supportive care requires a multidisciplinary approach, as AL is a multisystem disease and patients are often frail. Early death remains a major hurdle, due to extended cardiac disease, often as a result of delayed diagnosis.

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