Management of systemic AL amyloidosis: recommendations of the Myeloma Foundation of Australia Medical and Scientific Advisory Group

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Abstract
Systemic AL amyloidosis is a plasma cell dyscrasia with a characteristic clinical phenotype caused by multi-organ deposition of an amyloidogenic monoclonal protein. This condition poses a unique management challenge due to the complexity of the clinical presentation and the narrow therapeutic window of available therapies. Improved appreciation of the need for risk stratification, standardised use of sensitive laboratory testing for monitoring disease response, vigilant supportive care and the availability of newer agents with more favourable toxicity profiles have contributed to the improvement in treatment-related mortality and overall survival seen over the past decade. Nonetheless, with respect to the optimal management approach, there is a paucity of high-level clinical evidence due to the rarity of the disease, and enrolment in clinical trials is still the preferred approach where available. This review will summarise the Clinical Practice Guidelines on the Management of Systemic Light Chain (AL) Amyloidosis recently prepared by the Medical Scientific Advisory Group of the Myeloma Foundation of Australia. It is hoped that these guidelines will assist clinicians in better understanding and optimising the management of this difficult disease.
Introduction

Systemic AL amyloidosis is a rare protein misfolding and deposition disorder with an estimated annual incidence of ∼1 in 100 000 persons. It is unique among the various forms of systemic amyloidosis because the precursor protein is an immunoglobulin component, most commonly the lambda light chain, produced by a monoclonal plasma cell population in the bone marrow. The physicochemical properties of the protein cause it to misfold and adopt a characteristic beta-pleated sheet structure, leading to the formation of insoluble fibrils that accumulate as extracellular amyloid deposits in various tissues. Progressive infiltration of target organs leads to a constellation of clinical findings, including restrictive cardiomyopathy, the nephrotic syndrome and peripheral and autonomic neuropathy. Patients may also manifest with gastrointestinal symptoms, such as diarrhoea, bleeding and malabsorption, liver dysfunction and coagulopathy. Accurate diagnosis can sometimes be difficult, and readers are referred to recent reviews on this topic.

In an effort to assist clinicians in managing this condition, the Medical Scientific Advisory Group (MSAG) of the Myeloma Foundation has produced clinical guidelines on the management of AL amyloidosis (http://www.myeloma.org.au). These guidelines are based on available evidence from Phase I and II studies, retrospective analyses and expert opinion from practising haematologists on the MSAG panel. The key recommendations regarding staging, chemotherapy and supportive care will be summarised in this review and are graded according to standardised criteria.

Staging and prognosis

In the absence of effective treatment, patients with AL amyloidosis have a median survival of 1–2 years, but only 6 months if symptomatic cardiac involvement is present. However, it is now well recognised that patients with AL amyloidosis represent a diverse group with significant variation in treatment outcomes. This is mainly due to differences in the extent and severity of the disease at diagnosis that in turn impact on the tolerability of chemotherapy. Therefore, it is essential that a thorough evaluation be performed in all newly diagnosed patients to guide appropriate therapeutic decision-making.

Figure 1 outlines the suggested approach to the workup of AL amyloidosis. All patients should have their plasma cell clone carefully defined by serum and urine protein electrophoresis with immunofixation, serum free light chain assay and bone marrow examination with assessment of plasma cell clonality. In addition, the presence and degree of organ involvement should be assessed with particular attention to the heart, kidneys, liver, peripheral and autonomic nervous system and coagulation system. Of note, symptomatic myeloma should be excluded using radiological and bone marrow investigations (see MSAG guidelines) as these patients are best managed according to the principles of both AL amyloidosis and conventional myeloma practice. In selected patients, more detailed organ-specific investigations (such as cardiac magnetic resonance imaging and Holter monitor studies) may be required depending on the results of baseline tests.

Several clinical and biochemical parameters have been shown to carry prognostic significance in AL amyloidosis; of these, the presence and severity of cardiac involvement is the most powerful. All patients should have their disease staged according to the Mayo cardiac risk score which uses serum troponin T (TnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (Table 1). For laboratories offering alternative biomarkers, cardiac troponin I (TnI),7 high sensitivity TnT (hs-TnT)8 and BNP9 can be used, although these markers are not as extensively validated. This system classifies patients as stage I (low risk, eligible for aggressive therapies), stage II (intermediate risk) and stage III (high risk, characterised by high early mortality rates and significant toxicity with conventional treatments).

Principles of treatment

Contrary to common perception, amyloid deposition and resorption is a dynamic process. While therapies targeting serum amyloid P protein to enhance immune-mediated clearance of amyloid deposits are in clinical trials, current treatment approaches rely on reducing the amyloidogenic light chain which can produce regression of amyloid deposits, restoration of organ function and extension of survival. The goals of treatment of AL amyloidosis can be summarised in three points: (i) to reduce monoclonal protein production as profoundly and as quickly as possible to retard further amyloid deposition; (ii) to tailor therapy to the individual patient, taking into account the anticipated toxicities of various agents as they pertain to the extent and degree of organ involvement, as well as the availability of various agents; and (iii) to provide organ-specific supportive care to maximise quality of life and minimise treatment-related morbidity and mortality.

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Patients with both symptomatic myeloma and AL amyloidosis should be managed according to the principles of both conditions. For example, a young patient without contraindication to transplantation should receive induction, high-dose melphalan with stem cell support and maintenance in addition to bisphosphonates, whereas a young patient with cardiac amyloidosis where transplantation is contraindicated should not be transplanted, but may require a longer duration of therapy than if underlying symptomatic myeloma was not present.

Due to the complexity and rarity of this disease, referral to specialist centres that have experience in the management of AL amyloidosis is recommended. Enrolment in clinical trials is always preferable for these patients, owing to the lack of high-quality evidence to guide
optimal upfront treatment. The management of these patients should be coordinated by a specialist haematologist and conducted in a multidisciplinary setting.

**Choice of therapy**

Broadly speaking, any chemotherapy regimen with activity in multiple myeloma is likely to be effective in AL amyloidosis. Traditional approaches using oral melphalan and prednisolone produce modest survival benefit and have been superseded by the melphalan and dexamethasone combination. High-dose melphalan with autologous stem cell transplantation (HDM/ASCT) has been extensively studied and appears to produce more rapid control of the plasma cell clone with documented long-term overall survival at the expense of significant treatment-related morbidity and mortality. The immunomodulatory agents and proteasome inhibitors, which are standard therapies in myeloma, including thalidomide, lenalidomide and bortezomib, are demonstrating promising results in patients with AL amyloidosis in both the initial and relapsed/refractory disease settings.

Tables 2 and 3 summarise the MSAG recommendations when considering initial therapy options in AL amyloidosis. There is insufficient high-quality evidence available to recommend strongly a single particular therapeutic strategy; treatment decisions should instead be based on careful assessment of individual patient circumstance, the risks inherent in each approach and the availability of the various agents. In common with many organ diseases, access to all therapies is not universal in Australia due to both registration and reimbursement issues. These principles of treatment apply equally to the choice of therapy for relapsed or refractory disease.

### Table 1 Cardiac biomarker staging system for AL amyloidosis

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Threshold</th>
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<tbody>
<tr>
<td>Troponin TnT</td>
<td>&lt;0.035 mcg/L</td>
</tr>
<tr>
<td>Troponin TnI</td>
<td>&lt;0.1 mcg/L</td>
</tr>
<tr>
<td>Brain natriuretic peptide NT-ProBNP</td>
<td>&lt;332 ng/L</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt;100 ng/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Both troponin and BNP below threshold</td>
<td>26.4</td>
</tr>
<tr>
<td>Stage II</td>
<td>Either troponin or BNP above threshold</td>
<td>10.5</td>
</tr>
<tr>
<td>Stage III</td>
<td>Both troponin and BNP above threshold</td>
<td>3.5</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide; hs-TnT, high sensitivity troponin T; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TnI, troponin I; TnT, troponin T.

### Table 2 Considerations in the choice of initial therapy in AL amyloidosis

- Autologous stem cell transplantation (ASCT) should only be considered in carefully selected patients with minimal cardiac disease and adequate renal function (Level 2A, Grade B).
- In patients who may become candidates for ASCT, consideration should be given to the collection of PBSCT prior to extensive melphalan exposure (Level 2B, Grade C).
- Melphalan/dexamethasone, cyclophosphamide/thalidomide/dexamethasone (CTD), melphalan/bortezomib/dexamethasone (MDV) and cyclophosphamide/bortezomib/dexamethasone (CVD) are all suitable regimens for the initial treatment of AL amyloidosis. On the basis of promising Phase II data, bortezomib-based combinations (CVD, MDV) are the preferred upfront treatment strategy (Level 2A, Grade B).*

*At the time of writing, access to all recommended therapies is not universal in Australia.

### Treatment options

A brief discussion of the clinical evidence for various chemotherapy agents is presented below.

### Melphalan

Clinical trials of melphalan in AL amyloidosis were first reported in 1978. Melphalan and prednisolone produce modest survival benefit and have been superseded by the melphalan and dexamethasone combination. High-dose melphalan with autologous stem cell transplantation (HDM/ASCT) has been extensively studied and appears to produce more rapid control of the plasma cell clone with documented long-term overall survival at the expense of significant treatment-related morbidity and mortality. The immunomodulatory agents and proteasome inhibitors, which are standard therapies in myeloma, including thalidomide, lenalidomide and bortezomib, are demonstrating promising results in patients with AL amyloidosis in both the initial and relapsed/refractory disease settings.

Tables 2 and 3 summarise the MSAG recommendations when considering initial therapy options in AL amyloidosis. There is insufficient high-quality evidence available to recommend strongly a single particular therapeutic strategy; treatment decisions should instead be based on careful assessment of individual patient circumstance, the risks inherent in each approach and the availability of the various agents. In common with many organ diseases, access to all therapies is not universal in Australia due to both registration and reimbursement issues. These principles of treatment apply equally to the choice of therapy for relapsed or refractory disease.
Table 3  Recommendations for initial chemotherapy regimens in AL amyloidosis

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral melphalan-dexamethasone</td>
<td>Effective in patients with untreated or relapsed/refractory disease (Level 2A, Grade B).</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Combination regimens incorporating alkylating agents (such as cyclophosphamide/bortezomib/dexamethasone) produce higher response rates than monotherapy and are the preferred upfront treatment strategy, particularly for patients ineligible for ASCT (Level 2B, Grade B).</td>
</tr>
<tr>
<td>Belinostat</td>
<td>Weekly dosing schedules are better tolerated, but relative efficacy compared with standard dosing (d1, 4,8,11) is unknown (Level 2A, Grade C).</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Combination regimens are preferred in patients with renal impairment (Level 2B, Grade C).</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Bortezomib should be avoided in patients with Grade 3/4 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy (Level 2A, Grade C).</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Early-dose modification is required in the event of worsening neuropathy or autonomic symptoms (Level 2A, Grade B).</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Thalidomide should be avoided in patients with Grade 3 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy (Level 2B, Grade B).</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Due to cumulative neurotoxicity, thalidomide maintenance is not recommended (Level 2B, Grade C).</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Lenalidomide-based combination chemotherapy regimens are effective in patients with untreated or relapsed/refractory disease.</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Single agent lenalidomide has limited activity (Level 2A, Grade B).</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Thalidomide-based regimens should be avoided in patients with Grade 3 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy (Level 2B, Grade B).</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Due to cumulative neurotoxicity, thalidomide maintenance is not recommended (Level 2B, Grade C).</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Lenalidomide-based therapy should be considered in patients with peripheral or autonomic neuropathy that would preclude the use of other neurotoxic agents.</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>The initial maximum daily recommended lenalidomide dose, regardless of regimen, is 15 mg for 21 days of a 28-day cycle continued until progression (Level 2A, Grade B).</td>
</tr>
</tbody>
</table>

†At the time of writing, access to all recommended therapies is not universal in Australia. In the absence of toxicity, therapy duration is generally for six cycles (Fig. 2) or continuing treatment for two cycles beyond maximal response.

Bortezomib

Small phase I and II trials have reported rapid haematological responses with single agent bortezomib of up to 67%, while combination therapy with dexamethasone and alkylating agents has yielded overall HR and complete response (CR) rates of 81–94% and 42–71% respectively. Within the limitations of small patient numbers and retrospective study design, response rates superior to those seen in HDM/ASCT cohorts have been reported, with acceptable toxicity (most commonly peripheral and autonomic neuropathy). Importantly, there is preliminary evidence that patients with advanced cardiac disease, who traditionally do very badly regardless of treatment choice, may enjoy a survival benefit with the combination of cyclophosphamide/bortezomib/dexamethasone.19

It is still unclear whether the improved HR rates seen with bortezomib-based therapies will translate into an improvement in overall survival. Two matched case-control studies, published only in abstract form, demonstrate no significant improvement in overall survival with bortezomib-based regimens compared with cyclophosphamide/thalidomide/dexamethasone (CTD)20 or melphalan/dexamethasone.21 A multi-centre, randomised phase III trial comparing melphalan/dexamethasone with or without bortezomib in untreated, transplant-ineligible patients is currently underway to address this question. While basing treatment recommendations on the results of randomised studies is always preferable, current clinical data are consistent and promising enough to suggest that bortezomib-based regimens are the best available therapy for transplant ineligible patients. Further study will be required to determine if the short-term outcomes translate into long-term organ response and survival and whether outcomes will be superior to HDM/ASCT in transplant-eligible patients.

Other agents

Preliminary phase I and II studies of thalidomide in AL demonstrated HR rates around 50%, but were limited by significant dose-dependent toxicity, including bradycardia, peripheral oedema and rash.22,23 A study of thalidomide combined with CTD showed HR and CR rates of 74% and 21%, with organ responses in 26% and estimated median overall survival of 41 months.24 Toxicity of grade 3 or higher, necessitating dose reduction or treatment discontinuation, occurred in 24 (32%) patients. Patients aged over 70 years and those with New York
Heart Association class 2 or higher cardiac failure were treated with an attenuated CTD regimen, which produced less toxicity and similar response rates to the standard-dose regimen. Nonetheless, thalidomide-based regimens should be avoided in patients with grade 3 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy.

Lenalidomide-dexamethasone combinations produce similar response rates to thalidomide, with HR rates between 40% and 50% and CR rates up to 20%.25,26 Significant dose-limiting toxicities of lenalidomide include skin rash, renal impairment and cytopenias when used in doses above 15 mg daily.27 Combination regimens with cyclophosphamide and dexamethasone show HR rates of 55–60% with organ response rates of 22–31%,28,29 and may be particularly indicated in patients with amyloid neuropathy due to minimal neurotoxicity associated with this regimen.

New generation immunomodulatory drugs, such as pomalidomide, second generation proteasome inhibitors, such as carfilzomib and ixazomib, and the chemotherapeutic agent bendamustine are also currently under evaluation.

**High-dose melphalan/ASCT**

High-dose melphalan (200 mg/m²) conditioning with ASCT for AL was first reported in the 1990s. Early studies demonstrated deeper and more rapid haematological responses compared with conventional-dose chemotherapy, at the expense of significant treatment-related mortality between 20–30%.30 Peritransplant complications reported in AL patients include higher rates of gastrointestinal bleeding, fluid overload and malignant arrhythmias during stem cell mobilisation, particularly related to cyclophosphamide use.30,31 Since then, better understanding of the prejudicial effect of various pretransplant factors on patient survival has led to more refined selection criteria and consequent improvements in transplant-related mortality (Table 4). In particular, patients with cardiac involvement account for the majority of treatment-associated deaths, and exclusion of patients with elevated cardiac biomarkers (TnT > 0.06 mcg/L, TnI > 0.1 mcg/L or BNP > 300 ng/L) is now widely recommended.32,33 Renal impairment (glomerular filtration rate < 50 mL/min) is also a relative contraindication.34 As a result of this stringent patient selection, fewer than 25% of AL patients are considered suitable for HDM/ASCT at diagnosis.

Data from large, tertiary-referral transplant centres have shown haematological response rates as high as 76% with HDM/ASCT, with CR in up to 39% of cases.35,36 Organ response rates range from 47–63% with treatment-related mortality (TRM) rates of 10–12%, and more recently, as low as 5%.33 Extended follow-up confirms the survival benefit of a complete response, with median survival of 13.2 years in these patients compared with 3.2 years in those who fail to achieve a CR.36

**Figure 2** General treatment approach. (Key: 1 For patients in stable VGPR without organ response, consideration of second-line treatment is appropriate if prior therapy is well tolerated and alternative therapy is available. ASCT, high-dose melphalan with autologous stem cell transplantation; CR, complete response; PR, partial response; VGPR, very good partial response.)
The only randomised controlled trial to date comparing HDM/ASCT with conventional melphalan-dexamethasone therapy was published in 2007. One hundred patients aged 18–70 were randomised to the two treatment arms. Baseline characteristics were similar between groups, with cardiac involvement in approximately 50% of patients. Of 37/50 patients who underwent ASCT, the overall TRM was 24%. No significant difference in response rates was observed between the two groups. On intention-to-treat analysis, overall survival was significantly longer in the Mel-Dex arm (56.9 months vs 22.2 months, \( P = 0.04 \)). Despite criticism regarding the relatively high TRM rate, a landmark analysis at 6 months confirmed the survival benefit of Mel-Dex. In conjunction with a meta-analysis finding insufficient evidence of a survival benefit with HDM/ASCT, this trial has raised questions about the role of HDM/ASCT in upfront treatment of AL.

AL amyloidosis is usually associated with a low-level plasma cell clone, and there are currently no data to support a benefit from cytodestruction, such as that performed in myeloma before HDM/ASCT. Similarly, the role of HDM/ASCT to consolidate CR or very good partial response (VGPR; see Table 5 for definitions) following bortezomib-based induction is unknown.

### Response assessment

Regardless of which chemotherapeutic agent or combination is used, response assessment should be performed regularly using standardised haematological (HR) and organ response criteria (Table 4). The concept of HR is based on strong evidence that lowering of the involved free light chain (FLC) level correlates with improvements in cardiac function, histological amyloid regression and improved overall survival. The current international criteria use a novel parameter, the difference between involved and uninvolved free light chain (dFLC) which is only measurable if the baseline FLC level is >50 mg/L. It should be noted that all clinical validation of the utility of the FLC assay in monitoring response in AL has been done with the Freelite (The Binding Site, Birmingham, UK) assay. New FLC assays have recently been introduced, but their clinical validation will await further studies.

Organ responses take longer to occur and may not be appreciable for months to years after achieving a haematological response. Of particular importance is the role of NT-ProBNP or BNP in assessing cardiac response. A reduction in the NT-ProBNP of >30% and at least 300 ng/L, or 50 ng/L for BNP, is associated with significantly better overall survival. It should be noted that care must be taken with the interpretation of changes in the NT-ProBNP while the patient is on immunomodulatory drug therapy. Thus, assessment of response is best left until therapy is complete, and the patient has recovered from any therapy-related complications.

An overview of the recommended response-adapted approach to treatment of AL amyloidosis is presented in Figure 2. The achievement of CR or VGPR is associated with the most favourable survival outcomes and is the goal of therapy in all patients. There is emerging evidence to support early switch to second-line treatment in patients who fail to achieve at least VGPR after three cycles of initial therapy; however, there are no prospective data to show a survival advantage with this approach, and the authors recommend clinical discretion when considering change to second-line agents (e.g., patients with cardiac involvement who achieve partial haematological response with no organ response after three cycles have a greater urgency to achieve prompt reduction in the pathological light chain than patients with non-critical organ involvement). Likewise, in cases where a stable VGPR is achieved and treatment toxicities have been minimal, but there has been no organ response, it is reasonable to proceed to second-line therapy in an attempt to achieve CR.

**Table 4 Recommendations for autologous stem cell transplantation (ASCT)**

- **Patient selection**
  - Clinical factors
    - Age ≤ 65 years
    - New York Heart Association class I–II
    - ECOG performance status ≤ 2
    - Systolic blood pressure ≥ 90 mmHg
    - TnT < 0.06 mcg/L or Tnl < 0.1 mcg/L
    - BNP < 300 ng/L
    - Glomerular filtration rate > 50 ml/min
    - Bilirubin <1.5 x ULN with preserved hepatic synthetic function
  - Organ function
    - Peripheral blood progenitor cell mobilisation should be performed with G-CSF alone (Level 3, Grade C).
    - During stem cell reinfusion, cardiac monitoring is recommended for patients with cardiac involvement. Arrhythmia prophylaxis with amiodarone should be considered (Level 3, Grade C).
    - Dose-attenuated melphalan regimens are not recommended (Level 2B, Grade C).
    - Routine G-CSF is not recommended during the cytopenic period (Level 3, Grade C).
    - Higher platelet transfusion thresholds (>20 to 50 × 10^9/L) and daily testing for faecal occult blood during the cytopenic period is recommended (Level 3, Grade C).
    - Multidisciplinary care, particularly with cardiology and nephrology support, is essential (Level 3, Grade C).

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However, in cases where second-line agents are not available or are contraindicated, partial haematological response with organ response is a reasonable treatment target. Due to the biological and analytical variability of the FLC assay, care should be taken with decisions to change therapy based on haematological response when the baseline dFLC is low.

As the plasma cell burden is generally small in AL amyloidosis, there is no need for protracted duration of treatment as in myeloma. Generally, six cycles of treatment or treatment for two cycles beyond maximal response is adequate. There are currently no data to support ‘maintenance’ therapy in patients who have achieved an optimal response with the exception of lenalidomide-based regimens, which have generally been continued until progression.

### Supportive care

Careful medical management of amyloid-related complications is critical for the improvement of patient quality of life and the achievement of organ response. Recommendations are summarised in Table 6.

### Cardiac amyloid

The mainstay of supportive care for amyloid cardiomyopathy is the management of fluid overload using loop diuretics and/or spironolactone. Caution must be exercised in patients with concomitant autonomic neuropathy due to the risk of worsening orthostatic hypotension. Excessive diuresis can also exacerbate renal dysfunction in patients with renal amyloid. Although angiotensin-converting enzyme (ACE) inhibitors are used frequently in the management of heart failure, patients with cardiac amyloidosis rely on angiotensin for maintenance of blood pressure, and the use of these agents can induce severe hypotension. Similarly, beta-blockers and calcium-channel blockers are contraindicated due to the risk of hypotension and syncope relating to their negative inotropic effects.

Conduction disturbances and malignant arrhythmias may go undetected and result in sudden death. No randomised trial data are available to support the use of prophylactic antiarrhythmics in cardiac amyloid. However, some groups advocate amiodarone 200 mg/day if ventricular couplets or non-sustained ventricular tachycardia are detected on Holter monitor testing due to the association of these abnormalities with sudden death. Such patients are also highly sensitive to digoxin and are at risk of life-threatening arrhythmias, even at therapeutic concentrations, due to the high avidity of digoxin for amyloid fibrils resulting in increased intracardiac drug concentrations. The use of permanent pacemakers or implanted defibrillators may be beneficial in

<table>
<thead>
<tr>
<th>Table 5 Updated haematological and organ response criteria[^36]</th>
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<tbody>
<tr>
<td><strong>Haematological criteria</strong></td>
</tr>
<tr>
<td><strong>Response</strong></td>
</tr>
<tr>
<td>Complete response (CR)</td>
</tr>
<tr>
<td>Negative SPEP/IFE, UPEP/IFE, normal FLC ratio</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
</tr>
<tr>
<td>dFLC &lt; 40 mg/L</td>
</tr>
<tr>
<td>Partial response (PR)</td>
</tr>
<tr>
<td>dFLC decrease ≥ 50% (assessable in patients with baseline dFLC ≥ 50 mg/L)</td>
</tr>
<tr>
<td>No response (NR)</td>
</tr>
<tr>
<td>Less than PR</td>
</tr>
<tr>
<td>Progression</td>
</tr>
<tr>
<td>From CR, any detectable monoclonal protein or abnormal free light chain ratio (involved free light chain must be at least a doubling from the normal range).</td>
</tr>
<tr>
<td>From PR, 50% increase in serum M protein to &gt;5 g/L or 50% increase in urine M protein to &gt;200 mg/day (a visible peak must be present).</td>
</tr>
<tr>
<td>Or, FLC increase of 50% to &gt;100 mg/L at any time.</td>
</tr>
</tbody>
</table>

| **Organ criteria** |
| **Response** |
| **Progression** |
| Heart |
| NT-proBNP response >30% and >300 ng/L decrease in patients with baseline NT-proBNP ≥ 650 ng/L or NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4) |
| NT-proBNP increase (≥30% and >150 ng/L), or cTn increase ≥ 33%, or EF decrease ≥ 10% |
| Kidney |
| 50% decrease (at least 0.5 g/day) in 24-h urinary protein excretion (urine protein must be >0.5 g/day pretreatment). Creatinine and creatinine clearance must not worsen by 25% over baseline. |
| 50% increase (at least 1 g/day) in 24 h urinary protein to >1 g/day, or 25% worsening of serum creatinine or creatinine clearance. |
| Liver |
| 50% decrease in abnormal alkaline phosphatase value |
| 50% increase in alkaline phosphatase above the lowest value. |
| Peripheral nervous system |
| Improvement in electromyogram nerve conduction velocity |
| Progressive neuropathy by EMG or nerve conduction velocity |

[^36]: Weber et al. © 2014 Royal Australasian College of Physicians
selected patients with recurrent cardiogenic syncope or complex ventricular arrhythmias, but the expense of these devices may not be justified in cases that otherwise have a poor prognosis.

Cardiac transplantation for AL amyloidosis is rarely practised due to the contraindications of older age and multi-organ dysfunction. Nevertheless, small case series have been reported. It is clear from these studies that patients who do not undergo therapy to eradicate the plasma cell clone following transplantation will develop amyloid involvement and failure of the graft. Studies from various centres where cardiac transplantation has been combined with effective anti-plasma cell chemotherapy have reported 1-year overall survival around 80% with survival at 5 years dropping to around 60%, most often due to recurrent multi-organ amyloidosis.

### Renal amyloid

The medical management of the nephrotic syndrome generally relies on diuretic therapy to control symptomatic oedema and fluid overload. Loop diuretics are usually first line, but thiazides and other agents may also be required. ACE inhibitors may be used in patients without significant cardiac involvement or autonomic neuropathy to minimise proteinuria. Strict fluid and salt restriction and control of blood pressure and serum cholesterol are also recommended. Prophylactic anticoagulation should be considered on a case-by-case basis in patients with nephrotic syndrome, particularly those treated with an immunomodulatory agent, considering both benefits of thrombosis prevention and the bleeding diathesis that often occurs in AL amyloidosis.

Approximately one-third of patients with the nephrotic syndrome will proceed to dialysis. Overall survival in this group is improved (particularly in younger patients), and outcomes do not appear to differ between haemodialysis and peritoneal dialysis. Patients with cardiac involvement are more prone to hypotension and other complications related to volume changes during haemodialysis. Survival following initiation of dialysis is shorter in amyloidosis compared with other renal diseases. The vast majority of patients die from progressive cardiac involvement.

Renal transplantation for amyloid-related end-stage kidney disease is infrequently performed. Case reports and small case series suggest that renal transplantation, either before or following HDM/ASCT, may be able to improve dialysis-free and overall survival in carefully selected groups, such as those without cardiac involvement who achieve haematological complete remission after therapy.

### Orthostatic hypotension

The mechanisms underlying this common and disabling symptom relate to both impaired autonomic function and cardiac dysfunction. Inappropriate antihypertensive use and fluid depletion from diuretics may also contribute. Amyloid infiltration causing primary adrenal failure is uncommon, but patients should be screened for this complication with the short Synacthen test. For symptomatic orthostatic hypotension, lower limb compression garments can be used to augment venous return and assist in reducing peripheral oedema. Midodrine is an orally
active alpha-adrenergic agonist that can be started at 2.5 mg tds during the day and titrated to a maximum dose of 10 mg tds. Side-effects may include tachycardia, hypertension and restlessness. Fludrocortisone 100–200 mcg/day is less effective and often poorly tolerated due to fluid retention.

Gastrointestinal amyloid

Amyloid infiltration of the gastrointestinal tract may be subclinical or may present with weight loss, malabsorption or gastrointestinal bleeding. Motility disturbance, including constipation and diarrhoea, may result from concomitant autonomic neuropathy. A hierarchical approach using oral anti-motility agents, including loperamide and diphenoxylate, is often required. Long-acting or continuous subcutaneous octreotide has been used successfully in an outpatient setting in patients with severe diarrhoea.

Hepatic amyloidosis often presents initially with an asymptomatic elevation in the serum alkaline phosphatase reflecting intrahepatic cholestasis. Progression to cirrhosis and portal hypertension may occur if left untreated. Supportive management of AL liver disease should be along similar lines to other chronic liver diseases. The use of ursodeoxycholic acid has been reported in hepatic amyloid, but its role is yet to be defined. Similarly, insufficient evidence exists to guide the use of liver transplantation, but the general principles outlined above for renal and cardiac transplants would also apply to this approach.

Conclusion

AL amyloidosis can be a difficult condition to diagnose and is challenging to treat. Improvements in our appreciation of the importance of risk-adapted treatment approaches, the availability of newer agents and comprehensive supportive care strategies have led to better outcomes for these patients. Nonetheless there is an ongoing need for coordinated international trials that can accrue adequate numbers of patients to power meaningful phase III studies in order to clarify the many unanswered questions regarding ‘optimal’ upfront therapy. In the meantime, it is hoped that the availability of locally produced evidence-based guidelines will assist clinicians to care for patients with this devastating condition.

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