Clinical Practice Guideline

Management of Systemic AL Amyloidosis

Coordinated on behalf of the MSAG,
Dr Nicholas Weber and Associate Professor Peter Mollee

MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG) PANEL MEMBERS.

Bradley Augustson – WA
Ross Brown - NSW
Laurence Catley - QLD
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1. Introduction

In 2010, the first Clinical Practice Guidelines on the Management of Multiple Myeloma were published on behalf of the Medical Scientific Advisory Group of the Myeloma Foundation of Australia\(^1\). Unlike multiple myeloma, AL amyloidosis is a rare condition with limited high quality evidence to guide management and therefore limited consensus on what constitutes ‘standard’ treatment. The following guidelines have been prepared by the MSAG to provide Australian clinicians with a current, practical and evidence-based approach to the management of AL amyloidosis. Management of other types of amyloidosis is not covered by this review.

Levels of evidence and grades of recommendations used in these guidelines are listed in Table 1.

<table>
<thead>
<tr>
<th>LEVELS OF EVIDENCE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Evidence from meta-analysis of randomised controlled trials.</td>
</tr>
<tr>
<td>1B</td>
<td>Evidence from at least one randomised controlled trial.</td>
</tr>
<tr>
<td>2A</td>
<td>Evidence from at least one well-designed non-randomised trial, including phase II trials and case-control studies.</td>
</tr>
<tr>
<td>2B</td>
<td>Evidence from at least one other type of well-designed, quasi-experimental study such as observational studies.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence from well-designed non-experimental descriptive studies.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions and/or of respected authorities.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADES OF RECOMMENDATIONS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommendation based on at least randomised controlled trial of good quality addressing specific recommendation (Evidence level 1A and 1B).</td>
</tr>
<tr>
<td>B</td>
<td>Recommendation based on well-conducted studies but no randomised controlled trial on topic of recommendation (Evidence level 2A, 2B, and 3).</td>
</tr>
<tr>
<td>C</td>
<td>Recommendation based on expert opinions or reports (Evidence level 4).</td>
</tr>
</tbody>
</table>

2. Background

Systemic AL amyloidosis, previously called primary amyloidosis, is a protein misfolding and deposition disorder associated with a monoclonal gammopathy. The precursor protein is an immunoglobulin light chain fragment (most commonly the lambda chain) produced by a monoclonal plasma cell population in the bone marrow. Rarely, the precursor protein may be an immunoglobulin heavy chain (referred to as AH amyloidosis). These precursor proteins aggregate, taking on a beta-sheet secondary structure, into protofilaments and fibrils. The fibrils associate with serum amyloid P protein and other components such as glycosaminoglycans to form amyloid deposits in extracellular tissues that progressively accumulate and disrupt organ function. Whilst most monoclonal light chains are not amyloidogenic, it is currently not possible to predict those that are.

AL amyloidosis most commonly affects the heart, kidney and liver, with variable involvement of other organs (see Table 2). Progressive infiltration leads to organ dysfunction and end-stage complications including restrictive cardiomyopathy and the nephrotic syndrome. Involvement of the peripheral nervous system occurs in more than 20% of cases, causing a predominantly sensory peripheral neuropathy. Autonomic dysfunction may manifest various...
symptoms including orthostatic hypotension, gastrointestinal dysmotility and erectile dysfunction. Although generally considered to be pathognomonic of AL amyloidosis, macroglossia and periorbital ecchymosis are often absent.

The annual incidence of AL in the Australian population is unknown. The reported annual incidence in Europe and North America is around 1 in 100 000 persons\(^2\). The majority of cases are diagnosed over the age of 50 and there is a slight male predominance.

### Table 2: Incidence and updated definitions of organ involvement in AL amyloidosis (adapted from Merlini\(^3\), Gertz\(^4,5\))

<table>
<thead>
<tr>
<th>Organ</th>
<th>% of patients with involvement at diagnosis</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>65% (nephrotic 42%)</td>
<td>24-hr urine protein &gt; 500 mg/day, predominantly albumin</td>
</tr>
<tr>
<td>Heart</td>
<td>74% (heart failure 47%)</td>
<td>Echocardiogram: mean wall thickness &gt; 12 mm, no other cardiac cause, or NT-proBNP ≥332ng/L, in the absence of renal failure or atrial fibrillation.</td>
</tr>
<tr>
<td>Liver</td>
<td>17%</td>
<td>Total liver span &gt; 15 cm in the absence of heart failure or alkaline phosphatase &gt; 1.5 times institutional upper limit of normal</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>8%</td>
<td>Direct biopsy verification with symptoms</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Peripheral 15% Autonomic 14%</td>
<td>Peripheral: clinical diagnosis of symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration</td>
</tr>
<tr>
<td>Lung</td>
<td>NA</td>
<td>Direct biopsy verification with symptoms Interstitial radiographic pattern in absence of pulmonary oedema</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>17%</td>
<td>Macroglossia Arthropathy Claudication, presumed vascular amyloid Skin Myopathy by biopsy or pseudohypertrophy Lymph node (may be localized) Carpal tunnel syndrome</td>
</tr>
</tbody>
</table>

NT-proBNP, N-terminal pro-brain natriuretic peptide; NA, not available.

### Localised AL amyloidosis

Immunoglobulin light chain amyloidosis is most often systemic, that is where the production of the amyloid-forming light chain is distant to the amyloid deposits. Localised amyloidosis, in which amyloid deposits occur only at the site of light chain production, is another well-recognised entity. Localised AL amyloidosis is usually a non-life threatening disease with rare progression to systemic disease but frequent local recurrences\(^6\) AL-type deposits are thought to be produced by foci of low-grade monoclonal B-cells or plasma cells which secrete monoclonal immunoglobulin light chains in the immediate vicinity although in the majority of cases no histologically evident lymphoproliferative disease is present\(^7\) These amyloid deposits are commonly located in the tracheobronchial tree (causing dysphonia, cough, haemoptysis), orbit and adnexae, lung, bladder (haematuria), gastrointestinal tract,
lymph nodes and skin (plaques and nodules). Localised AL amyloidosis can, and has been reported to, occur in almost any organ of the body. It is also seen infiltrating plasmacytomas and in this situation is not necessarily indicative of systemic disease. Localised AL amyloidosis is treated with local surgical measures and is usually associated with an excellent prognosis although significant destruction of the involved organ can occur. There is no proven role for radiotherapy or chemotherapy in the routine management of these patients, although certain severe presentations (e.g. unresectable airway obstruction) may justify a trial of local radiotherapy.

3. Diagnostic workup

A new diagnosis of suspected AL amyloidosis requires: 1) confirmation of the diagnosis of amyloidosis, including determination that the amyloid subtype is of AL type; 2) evaluation of the plasma cell clone; and 3) evaluation of the extent and severity of organ involvement (see Figure 1).

1. Confirmation of the diagnosis

The diagnosis of AL amyloidosis can be complex and a detailed discussion is beyond the scope of these guidelines. A few points are worth emphasizing: firstly, early diagnosis is the key to effective management so the diagnosis of amyloidosis requires a high index of clinical suspicion when patients present with compatible systemic symptoms; secondly, Congo Red staining of a biopsy sample remains the gold standard diagnostic test for amyloidosis; and lastly, correct subtyping of amyloidosis is critical in all cases as the systemic amyloidoses (AL, AA, hereditary, senile) may have overlapping clinical features and occasionally non-AL amyloidosis occurs in the presence of an unrelated monoclonal gammopathy. This requires additional testing besides paraprotein detection (such as immunohistochemistry, genetic studies, tandem mass spectrometry) to determine with a high level of confidence that the amyloid deposits are composed of light chains. Readers are referred to recent guidelines on how to diagnose amyloidosis.

2. Evaluation of the plasma cell clone

As a disorder resulting from the proliferation of monoclonal plasma cells, AL amyloidosis can be considered a “forme fruste” of myeloma. Indeed, as defined by the International Myeloma Working Group criteria, the presence of amyloidosis is one of the features of end organ damage that may be used to confirm a diagnosis of symptomatic myeloma. Typical plasma cell myeloma (i.e. bone disease, hypercalcaemia, anaemia, marked marrow plasmacytosis) is complicated by systemic amyloidosis in 10-15% of cases, but few patients with AL amyloidosis will go on to develop myeloma. Whilst nearly all AL patients will have a detectable monoclonal immunoglobulin or serum free light chain at diagnosis, the absolute value is small and, in contrast to that seen in myeloma, typically remains stable over time. Up to 90% of cases have cytogenetic abnormalities including IgH gene rearrangements and deletions of 13q, with more recent data suggesting that the karyotypic abnormalities are more akin to myeloma than MGUS. Occasionally, patients will have an underlying lymphoproliferative disorder rather than a plasma cell dyscrasia.

Evaluation of the plasma cell clone is therefore important to define the underlying haematologic disease and to provide a baseline for response evaluation and prognostication. This will often have been performed as part of the diagnostic work-up.
Using currently available assays, almost all cases of AL amyloidosis will have a detectable circulating monoclonal protein. The combination of serum protein electrophoresis with immunofixation (SPEP/IFE), urine protein electrophoresis with immunofixation (UPEP/IFE), and serum free light chain assay (FLC) has a sensitivity > 95% for the detection of an abnormal plasma cell clone. All three assays should be performed in all cases.

Patients should be investigated to exclude end organ damage associated with multiple myeloma (refer to MSAG Clinical Practice Guideline: Multiple Myeloma). Skeletal imaging and assessment of bone marrow plasma cell percentage and clonality, serum biochemistry, renal function, and full blood count at diagnosis are recommended. Bone marrow FISH and karyotyping are not yet established in routine practice in AL amyloidosis. Those patients with underlying lymphoproliferative disease (e.g. Waldenstrom’s macroglobulinaemia) should be investigated accordingly.


AL amyloidosis is a multisystem disease and accurate baseline assessment plays an important role in planning treatment. Criteria for organ involvement in AL amyloidosis are listed in Table 2. A thorough clinical history and examination should be followed by relevant organ-specific investigations including the following:

- **Cardiac assessment**: electrocardiography, serum biomarkers and transthoracic echocardiography should be performed in all patients. Due to the variable availability of investigations, it is recommended that each institution choose a locally available serum biomarker combination of either BNP or NT-proBNP, and cTnl, cTnT or high sensitivity troponin for cardiac assessment. Echocardiographic features of AL include increased concentric left ventricular wall thickness with a preserved ejection fraction, bialtrial enlargement and restrictive filling patterns on Doppler studies, however no echocardiographic appearance is specific for amyloid heart disease. It should be noted that the classic ‘speckled’ appearance in the myocardium is a late feature and its absence by no means excludes significant cardiac involvement. Cardiac MRI can be an adjunct to the diagnosis of cardiac amyloidosis, particularly where other potential causes for cardiac dysfunction are present (e.g. ischaemic heart disease, hypertension); the characteristic pattern of global subendocardial late gadolinium enhancement is seen in up to 70% of cases. However, MRI is unable to discriminate between amyloid subtypes. A baseline 24 hour Holter monitor study is recommended in patients with cardiac involvement to assess the risk of clinically significant arrhythmias.

- **Renal assessment**: 24 hour urine protein studies (including total protein and immunofixation electrophoresis), serum creatinine and calculated glomerular filtration rate (GFR) should be performed in all patients.

- **Hepatic and gastrointestinal assessment**: liver function tests (particularly alkaline phosphatase) and clinical or imaging assessment of liver size are recommended at baseline. Patients presenting with gastrointestinal symptoms, particularly bleeding, should be assessed with endoscopy and colonoscopy both by direct visualization and with random biopsies.

- **Neurological assessment**: the diagnosis of amyloid neuropathy can be made on clinical grounds in a patient with other organ involvement, but nerve conduction studies and electromyography are recommended if there is diagnostic uncertainty.
• **Coagulation assessment**: a coagulation profile is recommended at baseline. Measurement of Factor X levels are indicated in those with abnormal coagulation test results as acquired factor X deficiency may occur presumably due to adsorption of factor X to amyloid fibrils.

• **Respiratory assessment**: patients presenting with pulmonary symptoms such as haemoptysis, cough and dyspnea should be investigated with computed tomography, respiratory function testing and, in selected cases, bronchoscopy with biopsy.

Scintigraphy with radionuclide-labelled serum amyloid P protein is a useful functional imaging technique with a sensitivity and specificity of >90% in AL amyloidosis\(^\text{16}\). Although it can underestimate cardiac involvement, SAP scintigraphy can provide a whole-body assessment of disease burden and may have applications in response evaluation\(^\text{17}\). However, this technique is not currently available in Australia and the majority of diagnostic and monitoring information required for patient management can be gained from other investigations.
Figure 1: Evaluation of newly-diagnosed AL amyloidosis

1. Define plasma cell clone
   - SPEP + IFE
   - FLC
   - 24hr urine UPEP + IFE
   - BMAT plus light chain clonality assessment (IHC or flow cytometry)

2. Assess for symptomatic myeloma
   (see MSAG Multiple Myeloma Guidelines for full details)
   - imaging to assess bone lesions
   - FBC, UEC, Ca2+

3. Assess organ involvement
   - Heart:
     - TnI or TnT or hsTnT
     - BNP or NT-proBNP
     - Echocardiogram
     - Electrocardiogram
   - Kidneys:
     - 24hr urinary protein and creatinine
   - Liver:
     - Liver span
     - LFT
   - Coagulation:
     - APTT, PT/INR
     - +/- factor X level
   - Neuropathy
     - Clinical assessment

4. Cardiac MRI
5. 24 hour Holter monitor
6. NCS + EMG
7. Upper endoscopy + colonoscopy (+ biopsy for Congo Red)
8. Respiratory function testing
9. CT chest
10. SAP scintigraphy (where available)

APTT, activated partial thromboplastin time; BMAT, bone marrow aspirate and trephine; BNP, brain natriuretic peptide; EMG, electromyography; FBC, full blood count; FLC, serum free light chain; hsTnT, high-sensitivity troponin T; IFE, immunofixation; IHC, immunohistochemistry; LFT, liver function tests; MRI, magnetic resonance imaging; NCS, nerve conduction studies; NT-proBNP, N-terminal pro-brain natriuretic peptide; PT, prothrombin time; SAP, serum amyloid P; SPEP, serum protein electrophoresis; TnT, troponin T; TnI, troponin I; UPEP, urine protein electrophoresis; UEC, urea, electrolytes and creatinine.
4. Prognostic factors

Prognostication in AL amyloidosis has evolved significantly in the past decade and forms an important basis for management decisions. Various clinical and biochemical factors have historically been associated with poor outcome as outlined in Table 3. However, it is now widely accepted that the key prognostic determinant in patients with AL amyloidosis is the presence and severity of cardiac involvement, best assessed by the cardiac biomarkers NT-ProBNP and troponin. Cardiac complications account for the majority of deaths in this population and patients with cardiac involvement experience shorter overall survival and higher rates of morbidity compared to patients with amyloid limited to other organs.18

<table>
<thead>
<tr>
<th>Table 3: Prognostic factors in AL amyloidosis</th>
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<tbody>
<tr>
<td><strong>Poor prognostic factors</strong></td>
</tr>
<tr>
<td>Cardiac factors</td>
</tr>
<tr>
<td>• High cardiac biomarker risk (see Table 3)</td>
</tr>
<tr>
<td>• Worse NYHA Classification score</td>
</tr>
<tr>
<td>• Syncope20</td>
</tr>
<tr>
<td>• Systolic blood pressure &lt;100mmHg21</td>
</tr>
<tr>
<td>• Clinical heart failure20, 22</td>
</tr>
<tr>
<td>• Pleural effusions20</td>
</tr>
<tr>
<td>• Reduced ejection fraction23</td>
</tr>
<tr>
<td>• Interventricular wall thickness &gt;15mm23</td>
</tr>
<tr>
<td>• Ventricular arrhythmias20</td>
</tr>
<tr>
<td>Measures of the plasma cell clone</td>
</tr>
<tr>
<td>• dFLC &gt; 180mg/L24</td>
</tr>
<tr>
<td>• Marrow plasmacytosis24</td>
</tr>
<tr>
<td>• High marrow plasma cell cyclin D1 expression25</td>
</tr>
<tr>
<td>• Cytogenetic abnormalities26</td>
</tr>
<tr>
<td>Other factors</td>
</tr>
<tr>
<td>• Worse performance status27</td>
</tr>
<tr>
<td>• More than two organs involved by amyloidosis28, 29</td>
</tr>
<tr>
<td>• Elevated urate30</td>
</tr>
<tr>
<td>• Elevated beta-2- microglobulin31</td>
</tr>
<tr>
<td>• Liver involvement32, 33</td>
</tr>
<tr>
<td>• Renal impairment (Cr Cl &lt;50mls/min)34</td>
</tr>
<tr>
<td>• Autonomic neuropathy35</td>
</tr>
</tbody>
</table>

All patients should have their cardiac biomarker risk calculated at diagnosis. The staging system devised by the Mayo group36 uses a reproducible assessment of cardiac function based on serum troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (see Table 4) and has been widely validated37, 38. For laboratories offering alternate biomarkers, cardiac troponin I (cTnI)36, high sensitivity cTnT (hs-cTNT)39 and BNP40 can be used although these markers are not as extensively validated. This system allows determination of patients as low risk (eligible for aggressive therapies such as autologous stem cell transplantation), intermediate risk and high risk (often die early prior to any
chance of response to therapy). It should be noted that within the Stage III group, those with a very high NT-ProBNP (>8500ng/L) or BNP (>800ng/L) have a particularly poor prognosis. NT-ProBNP and BNP levels are also raised in the presence of renal impairment.

<table>
<thead>
<tr>
<th>Table 4: Cardiac Biomarker Staging System for AL amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarkers</strong></td>
</tr>
<tr>
<td>Troponin</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Brain Natriuretic Peptide</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Median survival (mo)</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>

Whilst the cardiac biomarker staging system has provided the most robust system to assess prognosis, almost any measure of the severity of cardiac involvement predicts overall survival. This includes clinical parameters (New York Heart Association classification, hypotension, clinical heart failure, pleural effusions), echocardiographic parameters (low ejection fraction, thickened interventricular septum) and ventricular arrhythmias.

The serum free light chain concentration at diagnosis has also been established as a predictor of overall survival, best measured as the absolute difference between the involved and uninvolved FLC (dFLC). In a multivariate analysis incorporating cardiac biomarkers, Kumar et al. found patients with a dFLC > 180mg/L experienced significantly higher mortality (HR 1.4, p=0.01). Other plasma cell factors including the percentage of bone marrow plasma cells, bone marrow plasma cell cyclin D1 expression and the presence of cytogenetic abnormalities known to affect prognosis in multiple myeloma have also been shown to be prognostically significant.

5. Management

a. General considerations

Due to the rarity of AL amyloidosis, there is a paucity of randomised controlled trial data on which to base treatment recommendations. The evidence reviewed in this section is based primarily on phase I and II studies, retrospective analyses and expert opinion. There is a need for well-designed clinical trials in this field and enrolment of patients in such trials is strongly recommended wherever possible. Another difficulty to note is that there has been no consensus on whether to report responses to treatment in all patients (so called “intent-to-treat” analysis where those who die before response assessment are not excluded from response assessment) or only in evaluable patients (reflecting treatment efficacy but ignoring treatment toxicity). In the following sections we have calculated responses based on the “intent-to-treat” approach to give some consistency to the data.
Because of the complexity and rarity of this disease, referral to specialist centres that have experience in the management of AL amyloidosis is recommended. The management of these patients should be coordinated by a specialist haematologist and conducted in a multidisciplinary setting with involvement from relevant medical, allied health and other services including: clinical pathology and diagnostic radiology, cardiology, nephrology, gastroenterology, neurology, palliative care, pharmacy, nutrition/dietetics, haematology clinical nurse, social work and the primary care physician.

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treatment within the context of clinical trials is recommended where possible in all newly diagnosed patients.</td>
</tr>
<tr>
<td>• Referral to a tertiary centre with experience in the management of AL amyloidosis is recommended.</td>
</tr>
<tr>
<td>• Treatment within a multidisciplinary model incorporating medical specialties, allied health and social work staff is recommended.</td>
</tr>
</tbody>
</table>

**b. Response evaluation**

Survival in AL amyloidosis depends upon rapid reduction of the pathological immunoglobulin free light chain and stabilization or recovery of organ, particularly heart, function. Improvements in organ function can take many months to occur, so the initial assessment of treatment efficacy relies on measurement of haematologic response (HR).

**Haematologic response**

Absolute reductions in involved FLC levels have been shown to correlate with improved survival, regardless of treatment strategy. Left ventricular systolic function and serum NT-proBNP have been demonstrated to improve with lowering of the FLC, and histologic regression of amyloid deposits has been observed in patients who achieve normalization of the involved FLC post-treatment. Whilst earlier studies demonstrated a survival benefit with ≥50% reduction in the involved FLC, subsequent analyses reported superior survival when deeper FLC responses are achieved, either a dFLC reduction of 90% or absolute reduction to <40mg/L.

Haematologic response criteria produced by the International Symposium on Amyloid and Amyloidosis and recently updated are summarized in Table 5 and are somewhat similar to those used in myeloma with the categories Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR) and No Response (NR). Although negative serum and urine immunofixation electrophoresis is still required to meet criteria for CR, the updated criteria establish detectable dFLC as the principal measure of haematologic response. The threshold for measurable disease is dFLC ≥50mg/L; patients with levels below this at diagnosis are evaluable for CR only. The haematologic and cardiac response criteria were recently validated in a multicentre analysis which included a total of 1190 patients. 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) assay. New FLC assays have recently been introduced but their clinical validation will await further studies.
Organ Response

Organ Response Criteria are summarized in Table 5. Of particular importance is the role of NT-ProBNP or BNP in assessing cardiac response. A reduction in the NT-ProBNP (or BNP) of >30% and at least 300ng/L (or 50ng/L for BNP) is associated with significantly better overall survival. 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.

General recommendations for the frequency and timing of response assessments are presented in Table 6.

<table>
<thead>
<tr>
<th>Table 5: Updated Haematologic and Organ Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematologic criteria</strong></td>
</tr>
<tr>
<td>Complete response (CR)</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
</tr>
<tr>
<td>No response (NR)</td>
</tr>
</tbody>
</table>

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

cTn, cardiac troponin; dFLC, difference in free light chain concentration; EF, ejection fraction; FLC, free light chain concentration; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SPEP/IFE, serum protein electrophoresis and immunofixation; UPEP/IFE, urine protein electrophoresis and immunofixation.
Table 6: Recommended frequency of response assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>During chemotherapy</th>
<th>ASCT patients</th>
<th>During follow-up (all patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On completion of each cycle</td>
<td>Post-cycle 3 and cycle 6 only</td>
<td>Day 100</td>
</tr>
<tr>
<td>Full blood count</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ALP</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SPEP/IFE</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>UPEP/IFE (24 hr urine)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FLC</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>cTnI (or cTnT)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NT-proBNP (or BNP)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>24hr urinary total protein</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TTE (post cycle 6 only)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; ALP, alkaline phosphatase; SPEP/IFE, serum protein electrophoresis and immunofixation; UPEP/IFE, urine protein electrophoresis and immunofixation; FLC, serum free light chain concentration; dFLC, difference in free light chain concentration; TnT, troponin T; Tni, troponin I; NT-proBNP, N-terminal of pro-brain natriuretic peptide; BNP, brain natriuretic peptide; TTE, transthoracic echocardiogram.

c. Principles of treatment

The goals of treatment of AL amyloidosis can be summarised as follows:

a) To reduce monoclonal protein production as profoundly and as quickly as possible to retard further amyloid deposition. As discussed in the preceding section, the optimal haematologic endpoint is complete or very good partial response (≥90% reduction in dFLC or reduction in dFLC to <40mg/L), and if this is not possible, PR (≥50% reduction in dFLC) with organ response.

b) To tailor therapy to the individual patient, taking into account the anticipated toxicities of various agents as they relate to the extent and degree of organ involvement, as well as the availability of various agents.

c) Organ-specific supportive care to maximize quality of life and minimize treatment-related morbidity and mortality.

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.

An important caveat in the management of AL is that these patients are more frail and experience significantly higher treatment-related toxicity and mortality than patients with myeloma. Patients with AL amyloidosis more commonly present with multiorgan dysfunction, impaired nutrition and limited physiologic reserve that can make delivery of
chemotherapy extremely difficult. Therefore, treatment decisions should be made by careful assessment of patient-specific risks and benefits for each therapeutic strategy.

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 biphosphonates, 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.

An overview of the approach to treatment of AL amyloidosis is presented in Figure 2. The achievement of rapid and deep haematologic response is critical but not always possible. There is emerging evidence to support early switch to second-line treatment in patients who fail to achieve at least VGPR after 3 cycles of initial therapy however there is 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 haematologic response with no organ response after 3 cycles have a greater urgency to achieve prompt reduction in the pathologic 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. In cases where second line agents are not available or are contraindicated, however, partial haematologic response with organ response is a reasonable treatment target. Because of 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 (see Figure 2) or continuing treatment for two cycles beyond maximal response is adequate. There is 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.

While the optimal initial therapy for patients with AL amyloidosis has not yet been established, considerations for the choice of initial treatment are summarized in Table 7. The various chemotherapy regimens are discussed in the following sections and are detailed in Appendix 1. In common with many orphan diseases, access to all therapies is not universal in Australia due to both registration and reimbursement issues.
Table 7: Considerations in the choice of initial therapy in AL amyloidosis

- MDex, CTD, MDV and 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)*
- Autologous stem cell transplantation (ASCT) should only be considered in carefully selected patients with minimal cardiac disease and adequate renal function (GFR>50ml/min) (Level 2A, Grade B)
- In patients who may become candidates for ASCT, consideration should be given to the collection of PBSC prior to extensive melphalan exposure (Level 2B, Grade C)
- Bortezomib and thalidomide-based regimens should be avoided in patients with Grade 3 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy (Level 2B, Grade B)
- Bortezomib-based regimens are preferred in patients with renal impairment (Level 2B, Grade C)

*At the time of writing, access to all recommended therapies is not universal in Australia
d. Chemotherapy and novel agents

**Melphalan**

Clinical trials of melphalan in AL amyloidosis were first reported in 1978. Melphalan and prednisolone (MP) demonstrated superior haematologic and organ responses with minor survival improvement in prospective randomized trials when compared to placebo or colchicine\(^6\). Following recognition of the efficacy of high-dose dexamethasone in AL amyloidosis, the melphalan-dexamethasone regimen (Mel-Dex) was developed (Table 8). Trials in autologous transplant-ineligible patients treated with melphalan 0.22mg/kg and dexamethasone 40mg on days 1-4 every 28 days have yielded HR and OR rates between 52-67% and 34-48% respectively with minimal reported treatment-related mortality. Further evidence for the efficacy of this regimen came with the randomized trial comparing Mel-Dex with ASCT by Jaccard et al\(^6\), which found a significant survival benefit in the Mel-Dex group (56.9mo vs. 22.2mo, p=0.04).

Due to concerns about the potential for erratic absorption of oral melphalan in AL patients, some centres have used intravenous administration. A phase II Australian study assessed monthly IV melphalan and oral dexamethasone in patients ineligible for HDM/ASCT. IV melphalan at a dose of 20mg/m\(^2\) was associated with high rates of grade 3&4 myelosuppression and corresponding high treatment-related mortality rates, with no improvements in response\(^6\). IV melphalan at 16mg/m\(^2\) appears to be more tolerable\(^27\).

---

**Table 8: Major trials of conventional dose melphalan in AL amyloidosis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Study design</th>
<th>N</th>
<th>HR (CR) %(^a)</th>
<th>OR %(^a)</th>
<th>Median OS (months)</th>
<th>TRM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyle 1997(^62)</td>
<td>MP ± colchicine</td>
<td>RCT</td>
<td>220</td>
<td>28</td>
<td>17</td>
<td>18</td>
<td>-</td>
<td>Myelodysplasia occurred in ~5% of mel group</td>
</tr>
<tr>
<td>Palladini 2004, 2007(^65,)(^66)</td>
<td>Mel-Dex</td>
<td>Phase II single centre</td>
<td>46</td>
<td>67 (33)</td>
<td>48</td>
<td>61.2</td>
<td>4%</td>
<td>Pts ineligible for ASCT; Median 4 cycles completed</td>
</tr>
<tr>
<td>Jaccard 2007(^63)</td>
<td>Mel-Dex</td>
<td>Phase III RCT</td>
<td>50</td>
<td>52 (18)</td>
<td>34</td>
<td>57</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mollee 2012(^64)</td>
<td>IV Mel-Dex</td>
<td>Phase II, multcentre</td>
<td>14</td>
<td>21 (7)</td>
<td>7</td>
<td>6.8</td>
<td>50% at 6mo</td>
<td></td>
</tr>
<tr>
<td>Lebovic 2008(^67)</td>
<td>Mel-Dex</td>
<td>Retrospective, single centre</td>
<td>40</td>
<td>58 (13)</td>
<td>-</td>
<td>10.5</td>
<td>-</td>
<td>Pts ineligible for ASCT</td>
</tr>
</tbody>
</table>

\(^a\) Calculated by intention-to-treat

ASCT, autologous stem cell transplant; HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; RCT, randomized controlled trial; TRM, treatment-related mortality.

**Recommendations**^\(^*\)

- Oral melphalan-dexamethasone is a suitable first-line regimen (Level 1B, Grade A).

^\(^*\)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 (see Figure 2) or continuing treatment for two cycles beyond maximal response

**Bortezomib**

Preliminary data suggests that bortezomib is the most active agent in AL amyloidosis. The high response rates seen with this drug are postulated to occur due to the particular susceptibility of clonal AL plasma cells to the effects of proteasome inhibition, in turn due to the endoplasmic reticulum stress induced by accumulation of toxic unfolded amyloidogenic light chains.

Major trials of bortezomib in AL amyloidosis are summarized in Table 9. Haematologic response rates with single agent or combined therapy are not only high but also rapid, with median time to HR of 52 days in one study. Whilst twice weekly dosing may improve the depth of response, this appears to be at the expense of increased toxicity, including thrombocytopenia and peripheral neuropathy. Patients with significant (Grade 3) or painful sensory neuropathy and significant autonomic neuropathy were excluded from these trials. Because of neuropathic effects, autonomic complications including postural hypotension and diarrhoea can be problematic and need careful monitoring and should prompt early dose modification of bortezomib.

Alkylator-bortezomib combinations appear to provide even higher response rates, as evidenced by two recent studies which enrolled both untreated and relapsed patients. 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 limited toxicity (most commonly peripheral and autonomic neuropathy). Additionally, there is preliminary evidence that patients with advanced cardiac disease, who traditionally do very badly regardless of treatment choice, may enjoy prolonged overall survival with the CVD regimen.

Two matched case-control studies published only in abstract form demonstrate no significant improvement in overall survival with bortezomib-based regimens compared to CTDo or MDex. A multicentre, randomized phase III trial comparing Mel-Dex with or without bortezomib in untreated, transplant-ineligible patients is underway. While basing treatment recommendations on the results of randomized 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.

<table>
<thead>
<tr>
<th>Table 9: Major trials of bortezomib in AL amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Kastritis 2010&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reece 2011&lt;sup&gt;70&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Mikhael 2012\textsuperscript{71} & CVD & Retrospective single centre & 17 & 94 (71) & 50\% (renal) 71\% (cardiac) & NR & Majority (88\%) received weekly bortezomib; no grade 3/4 peripheral neuropathy \\
Venner 2012\textsuperscript{38} & CVD & Retrospective single centre & 43 & 81 (42) & 46 & NR & 46\% stage III 2yr OS 98\% (94\% for stage III patients) 14\% discontinued treatment due to neuropathy \\
Zonder 2009\textsuperscript{74} & MDV & Prospective phase II & 30 & 94 (63) & 40 & NR & 7 had symptomatic improvement in neuropathy \\

\textsuperscript{a}Calculated by intention-to-treat; NR = not reached. 
HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; TRM, treatment-related mortality.

**Recommendations**\textsuperscript{\textsuperscript{a}}

- Bortezomib-based chemotherapy regimens are effective in patients with untreated or relapsed/refractory disease (Level 2A, Grade B).
- Combination regimens incorporating alkylating agents, such as CVD, produce higher response rates than monotherapy and are the preferred upfront treatment strategy, particularly for patients ineligible for HDM/ASCT (Level 2B, Grade B).
- Weekly dosing schedules are better tolerated but relative efficacy compared to standard dosing (d1,4,8,11) is unknown (Level 2A, Grade C).
- Bortezomib should be avoided in patients with Grade 3 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy (Level 2A, Grade C).
- Early dose modification is required in the event of worsening neuropathy of autonomic symptoms (Level 2A, Grade B)

\textsuperscript{a}At the time of writing, access to all recommended therapies is not universal in Australia

\textsuperscript{\textsuperscript{a}}In the absence of toxicity, therapy duration is generally for six cycles (see Figure 2) or continuing treatment for two cycles beyond maximal response

**Thalidomide**

Thalidomide has been studied as a single agent or in combination with other agents in a number of small single-centre trials (see Table 10). Significant treatment-limiting toxicity has been observed with doses above 100mg daily, including symptomatic bradycardia, peripheral oedema, rash and cognitive side-effects. Attenuated dose thalidomide in combination with cyclophosphamide and low-dose dexamethasone (CTD\textsubscript{a}) appears to produce the highest response rates with acceptable toxicity\textsuperscript{75}. A retrospective comparison of Mel-Dex and CTD\textsubscript{a} found no difference in efficacy between the two regimens\textsuperscript{76}. Due to cumulative neurotoxicity use of thalidomide as maintenance therapy is not recommended. Likewise, thalidomide-based regimens should be avoided in patients with Grade 3/4 peripheral sensory neuropathy, painful neuropathy or significant autonomic neuropathy.

**Table 10: Major trials of thalidomide in AL amyloidosis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Study design</th>
<th>N</th>
<th>HR (CR) % \textsuperscript{a}</th>
<th>OR % \textsuperscript{a}</th>
<th>Median OS (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palladini</td>
<td>Thal-dex</td>
<td>Phase</td>
<td>31</td>
<td>48 (19)</td>
<td>26</td>
<td>-</td>
<td>≥Grade 3 toxicity in 65%, most</td>
</tr>
</tbody>
</table>
2005

<table>
<thead>
<tr>
<th>2005</th>
<th>I/II</th>
<th>commonly symptomatic bradycardia</th>
</tr>
</thead>
</table>

| Wechalekar 2007 | CTD/CTDa | Phase II | 75 | 74 (21) | 26 | NR | Nonsignificant difference between CTD and CTDa. ≥Grade 3 toxicity in 32%. |
| Palladini 2009 | MTD | Phase II | 22 | 36 (5) | 18 | 5.3 | 100% of patients were NYHA Class IV |

*^\text{Calculated by intention-to-treat}; NR = not reached.
HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; TRM, treatment-related mortality.

**Recommendations**

- CTD/CTDa is a suitable first-line regimen (Level 2A, Grade B).
- The maximum daily recommended thalidomide dose, regardless of regimen, is 100mg (Level 2B, Grade C).
- Due to cumulative neurotoxicity, thalidomide maintenance is not recommended (Level 2B, Grade C).

*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 (see Figure 2) or continuing treatment for two cycles beyond maximal response

**Lenalidomide**

Despite poor results seen with lenalidomide monotherapy in earlier studies, doublet and triplet combinations have shown promising response rates (see Table 11). Early trials of lenalidomide using ‘myeloma’ doses (ie 25mg daily) in combination with dexamethasone demonstrated HR rates around 40-50% but with significant haematologic, renal and skin toxicity. Subsequently, a daily lenalidomide dose of 15mg was established as the maximum tolerated dose in a phase I/II dose escalation study. Using this lower dose, haematologic response rates around 60% have been reported with the combination of lenalidomide, cyclophosphamide, and dexamethasone although the CR rate has remained disappointingly low. There is preliminary evidence that lenalidomide should be continued after achievement of maximal response in a maintenance fashion to improve organ responses.

Unlike the other novel agents, lenalidomide does not appear to induce or exacerbate neuropathy in AL patients; for this reason, lenalidomide-based regimens are particularly suitable for patients with amyloid neuropathy. Finally, some groups have reported discrepant increases in BNP and NT-proBNP levels in patients treated with lenalidomide. This appears to be independent of changes in renal function and FLC and may interfere with the assessment of cardiac response in this patient group.

**Table 11: Major trials of lenalidomide in AL amyloidosis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Study design</th>
<th>N</th>
<th>HR (CR) % a</th>
<th>OR % a</th>
<th>Median OS (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanchorawala 2007</td>
<td>RD</td>
<td>Phase II</td>
<td>34</td>
<td>47 (21)</td>
<td>21</td>
<td>NR</td>
<td>≥Grade 3 myelosuppression in 35%</td>
</tr>
<tr>
<td>Dispenceri</td>
<td>RD</td>
<td>Phase II</td>
<td>22</td>
<td>41 (5)</td>
<td>23</td>
<td>NR</td>
<td>Only 55% completed &gt;3</td>
</tr>
</tbody>
</table>
Recommendations*

- Lenalidomide-based combination chemotherapy regimens are effective in patients with untreated or relapsed/refractory disease. Single agent lenalidomide has limited activity (Level 2A, Grade B).
- Combination regimens incorporating alkylating agents, such as CRd and MRd, are a reasonable treatment strategy for relapsed patients, subject to local availability of lenalidomide (Level 2A, Grade B).
- Lenalidomide-based therapy should be considered in patients with peripheral or autonomic neuropathy which would preclude the use of other neurotoxic agents.
- The maximum daily recommended lenalidomide dose, regardless of regimen, is 15mg for 21 days of a 28 day cycle (Level 2A, Grade B).

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

Other agents

Pomalidomide is a third-generation immunomodulatory agent with activity in multiple myeloma. A single phase II trial of pomalidomide in combination with weekly dexamethasone in previously treated patients with AL amyloid showed a HR rate of 48% with organ responses in 5/33 patients. The most common adverse effects were fatigue and neutropenia. Second generation proteasome inhibitors such as carfilzomib and ixazomib, and the chemotherapeutic agent bendamustine are also currently under evaluation.

e. Autologous stem cell transplantation

Background

Evidence supporting the use of high-dose therapy with autologous stem cell transplantation for AL amyloidosis first emerged in 1996. The current literature base is limited, with the majority of evidence derived from single-centre case series and small phase II trials. Results from earlier trials showed significant improvements in outcomes compared with standard melphalan-based chemotherapy, with overall response rates around 60% and median OS
around 5 years. However, treatment-related mortality (TRM) was significantly higher than that observed in the myeloma population, with figures varying between 20-40%. Larger, more experienced centres have achieved improvements in TRM (around 10-15%) with careful patient selection. Response rates have not improved dramatically but haematologic response and survival following ASCT have been shown to be durable with follow-up now exceeding 10 years (see Table 12).

‘Risk-adapted’ conditioning with reduced-dose melphalan (100-140mg/m2) is often applied to patients who are considered to be at higher risk from transplant-related complications, traditionally because of advanced age, renal impairment or cardiac dysfunction. Retrospective analyses from two large centres have shown that such dose reductions produce inferior response rates with similar toxicities compared with high-dose melphalan.

The only randomized trial to date comparing HDM/ASCT and chemotherapy with melphalan-dexamethasone was published by Jaccard et al in 2007. One hundred patients aged 18-70 were randomized to each treatment arm. Baseline characteristics were similar between groups, with cardiac involvement in approximately 50% of patients. Of 37/50 patients who underwent ASCT, 10 received modified dose conditioning with melphalan 140mg/m2; the overall TRM in the transplant arm 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 (56.9mo vs. 22.2mo, p=0.04). The authors concluded that outcomes with HDM/ASCT were not superior to those with Mel-Dex. Subsequently, a meta-analysis of 12 studies comparing ASCT with conventional chemotherapy concluded that while ASCT does not appear to confer an overall survival benefit, the low quality of available evidence indicates that further studies are needed to resolve the question. Critics of the study by Jaccard et al pointed out that the reported TRM is considerably higher than that reported by experienced transplant centres, and that the use of dose-attenuated melphalan conditioning was inappropriate due to its demonstrated inferiority compared with high-dose treatment. Nonetheless, this study has raised important questions about the need to assess risk carefully when considering HDM/ASCT versus conventional chemotherapy upfront.

Table 12: Major trials of HDM/ASCT in AL amyloidosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>N</th>
<th>HR (CR) %</th>
<th>OR %</th>
<th>Median OS (months)</th>
<th>TRM %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner, 2004</td>
<td>Single centre, prospective</td>
<td>421</td>
<td>(34)</td>
<td>51</td>
<td>75.6</td>
<td>11</td>
<td>45% received modified dose melphalan</td>
</tr>
<tr>
<td>Cibeira 2011</td>
<td>Retrospective, single centre</td>
<td>434</td>
<td>(76)</td>
<td>47</td>
<td>32-NR</td>
<td>10</td>
<td>1996-2010 38% received modified dose melphalan 25% stage III</td>
</tr>
<tr>
<td>Gertz, 2010</td>
<td>Phase III RCT</td>
<td>50</td>
<td>(36)</td>
<td>26</td>
<td>22</td>
<td>24</td>
<td>13/50 (26%) did not receive assigned intervention in HDM/ASCT arm 27% received modified dose melphalan; 58% 3yr OS</td>
</tr>
<tr>
<td>Jaccard 2007</td>
<td>Retrospective, single centre</td>
<td>100</td>
<td>(79)</td>
<td>43</td>
<td>NR</td>
<td>3</td>
<td>55 patients received VAD or high-dose dexamethasone induction pre-ASCT</td>
</tr>
<tr>
<td>Mangatter 2008</td>
<td>Retrospective, single centre</td>
<td>50</td>
<td>(36)</td>
<td>26</td>
<td>22</td>
<td>24</td>
<td>13/50 (26%) did not receive assigned intervention in HDM/ASCT arm 27% received modified dose melphalan; 58% 3yr OS</td>
</tr>
</tbody>
</table>

Comments
Eligibility criteria for autologous stem cell transplantation

Selection criteria for HDM/ASCT vary between institutions and consensus guidelines have not been devised. In general, conventional eligibility criteria for ASCT, such as age and performance status, should be assessed in conjunction with amyloid-specific factors including organ (especially cardiac) involvement and susceptibility to treatment toxicity.

Commonly used eligibility criteria for HDM/ASCT are listed in Table 13. The presence and degree of cardiac involvement is the most significant parameter in predicting TRM. Traditional markers such as left ventricular ejection fraction and interventricular septal thickness have been superseded by the use of cardiac biomarkers. The Mayo Clinic cardiac biomarker-based staging system has been validated in a cohort of 99 transplant patients, with the analysis revealing significantly higher 90-day mortality in patients with elevated baseline cardiac troponin I. A subsequent analysis showed significantly higher 100-day all-cause mortality (28% vs 7%) in patients with baseline cTnT ≥0.06mcg/L compared to those with cTnT <0.06mcg/L. In essence, patients with significant cardiac involvement are not candidates for upfront HDM/ASCT.

<table>
<thead>
<tr>
<th>Vesole 2006(^{95})</th>
<th>Registry study</th>
<th>107</th>
<th>32 (16)</th>
<th>-</th>
<th>47.2</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodman 2006(^{96})</td>
<td>Retrospective, multicentre</td>
<td>92</td>
<td>37 (20)</td>
<td>-</td>
<td>63.6</td>
<td>23</td>
</tr>
<tr>
<td>Moreau, 1998(^{28})</td>
<td>Retrospective, multicentre</td>
<td>21 (14)</td>
<td>48</td>
<td>-</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Mollee, 2004(^{21})</td>
<td>Retrospective, single centre</td>
<td>20</td>
<td>56 (28)</td>
<td>-</td>
<td>60</td>
<td>35</td>
</tr>
</tbody>
</table>

\(^{a}\) Calculated by intention-to-treat;
HDM/ASCT, high dose melphalan with autologous stem cell transplantation; HR, haematologic response; CR, complete response; OR, organ response; OS, overall survival; TRM, treatment-related mortality; NR, not reached.

<table>
<thead>
<tr>
<th>Table 13: Commonly used eligibility criteria for autologous stem cell transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical factors</strong>(^{90})</td>
</tr>
<tr>
<td>• Age ≤65</td>
</tr>
<tr>
<td>• NYHA class I-II</td>
</tr>
<tr>
<td>• ECOG performance status ≤ 2</td>
</tr>
<tr>
<td>• Systolic blood pressure ≥90mmHg</td>
</tr>
<tr>
<td><strong>Organ function</strong></td>
</tr>
<tr>
<td>• cTnT &lt;0.06mcg/L or cTnI &lt;0.1mcg/L(^{97})</td>
</tr>
<tr>
<td>• BNP &lt;300ng/L(^{98})</td>
</tr>
<tr>
<td>• GFR &gt;50ml/min(^{50})</td>
</tr>
<tr>
<td>• Bilirubin &lt;1.5 x ULN with preserved hepatic synthetic function</td>
</tr>
</tbody>
</table>

Induction therapy before autologous stem cell transplantation

AL is usually associated with a low-level plasma cell clone and there is currently no data to support a benefit from cyto reduction before HDM/ASCT. A randomized prospective trial addressing this issue, albeit with suboptimal induction therapy of melphalan and prednisolone, showed that pre-ASCT cytoreduction is likely to allow disease progression with no benefit in responses or survival\(^{99}\). In a subsequent study, of patients who received two cycles of bortezomib-based pre-transplant induction therapy, 14% who were eligible for
transplantation at enrollment, did not proceed to transplantation due to clinical deterioration during induction treatment. At the current time, the role of novel agents in pretransplant cytoreduction is unclear. Similarly, the role of HDM/ASCT to consolidate CR or VGPR following bortezomib-based induction is unknown.

**Stem cell collection**

Patients with AL amyloidosis experience higher rates of complications and mortality during peripheral blood stem cell mobilization and collection, with the overall complication rate around 15%\(^\text{10}\). Peripheral and pulmonary oedema, symptomatic hypocalcaemia and hypoxia are all more common and can jeopardise the collection procedure. Cyclophosphamide use is associated with more toxicity and higher rates of hospitalization and cardiac complications than G-CSF alone. Therefore, stem cell mobilization with G-CSF 10mcg/kg alone is recommended, given in twice daily divided doses with collection beginning on day 5.

**Peritransplant care**

Precautions specific to this patient group include:

- **Arrhythmia prophylaxis.** Patients with cardiac involvement are at high risk of life-threatening arrhythmias including atrial tachycardias and non-sustained ventricular tachycardia around the time of stem cell collection, reinfusion and cytopenic phase.\(^\text{101}\). Cardiac monitoring during stem cell reinfusion is recommended in these patients.\(^\text{102}\) The use of prophylactic antiarrhythmics, such as amiodarone, should be considered.
- **Careful attention to fluid balance.** G-CSF should be avoided in patients with nephrotic syndrome and cardiac involvement due to risk of fluid retention; albumin replacement should be considered if serum albumin <20g/L, and low-salt fluids for blood pressure support if required.
- **Increased risk of GI bleeding.** Careful pre-transplant assessment is required, including stool fecal occult blood testing and targeted endoscopic evaluation of the upper and lower bowel if GIT involvement is suspected. During the cytopenic phase, routine proton-pump inhibitor therapy, higher platelet transfusion threshold (>20 to 50 x 10\(^9\)/L) and daily testing of the faeces for blood are recommended.
- **Higher rates of nausea and vomiting.** This is thought to result from impaired gastric emptying and may require higher doses and longer duration of antiemetics.
- **Infection prophylaxis as per local guidelines.**

<table>
<thead>
<tr>
<th><strong>Recommendations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- High-dose melphalan (200mg/m(^2)) with autologous stem cell transplantation is an effective front-line therapy in selected untreated patients (Level 2B, Grade B).</td>
</tr>
<tr>
<td>- Dose-attenuated melphalan regimens are not recommended (Level 2B, Grade C).</td>
</tr>
<tr>
<td>- Eligibility criteria for HDM/ASCT should be based primarily on cardiac status; patients with elevated cardiac biomarkers (cTnT &gt;0.06mcg/L, cTnl &gt;0.1mcg/L, or BNP &gt;300ng/L) should be excluded. Renal impairment (GFR &lt;50mls/min) is also a relative contraindication (Level 2B, Grade B)</td>
</tr>
<tr>
<td>- Peripheral blood progenitor cell mobilization should be performed with G-CSF alone (Level 3, Grade C).</td>
</tr>
<tr>
<td>- During stem cell reinfusion, cardiac monitoring is recommended for patients with cardiac involvement. Arrhythmia prophylaxis with amiodarone should be considered (Level 3, Grade C).</td>
</tr>
<tr>
<td>- Routine G-CSF is not recommended during the cytopenic period (Level 3, Grade C).</td>
</tr>
</tbody>
</table>
• Higher platelet transfusion thresholds (>20 to 50 x 10^9/L) and daily testing for faecal occult blood during the cytopenic period is recommended (Level 3, Grade C).
• Multi-disciplinary care, particularly with cardiology and nephrology support, is essential.

f. 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.

Cardiac amyloid

As in other infiltrative cardiomyopathies, cardiac amyloidosis is characterized by diastolic dysfunction that, with time, progresses to produce a restrictive cardiomyopathy with abnormal systolic function. The mainstay of supportive care in cardiac amyloid is the management of fluid overload using loop diuretics and/or spironolactone\(^{103}\). 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\(^{104}\). Similarly, beta-blockers and calcium-channel blockers are contraindicated due to the risk of hypotension and syncope relating to their negative inotropic effects.

Cardiac amyloid deposition within electrical pathways frequently causes conduction disturbances and malignant arrhythmias that may go undetected and result in sudden death. One study of 333 patients with cardiac amyloid (including 199 with AL) found significant arrhythmias in 19.5% when screened with 24 hour Holter monitoring\(^{105}\). No randomized trial data is available to support the use of prophylactic antiarrhythmics in cardiac amyloid; some groups, however, advocate amiodarone 200mg/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\(^{65}\). 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\(^{104}\). The use of permanent pacemakers or implanted defibrillators may be beneficial in selected patients with recurrent cardiogenic syncope or complex ventricular arrhythmias\(^{106}\), 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 practiced due to the contraindications of older age and multiorgan 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 employing this approach have reported 1-year OS around 80% with survival at 5 years dropping to around 60%, most often due to recurrent multiorgan amyloidosis\(^{107,108}\).

<table>
<thead>
<tr>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>• Symptomatic cardiac failure should be managed with loop diuretics and potassium-sparing diuretics (Level 3, Grade C).</td>
</tr>
<tr>
<td>• ACE inhibitors, beta-blockers and calcium-channel blockers should be avoided,</td>
</tr>
</tbody>
</table>
particularly in patients with autonomic neuropathy, impaired renal function and baseline hypotension (Level 3, Grade C).

- Digoxin is relatively contraindicated for control of atrial fibrillation (Level 3, Grade C).
- Primary arrhythmia prophylaxis with amiodarone may be considered in patients with high-risk features on Holter monitor testing (Level 3, Grade C).
- Cardiac transplantation may be considered for highly selected patients with severe cardiac disease and without other organ involvement, and should be followed by chemotherapy with the intention of achieving at least a partial haematologic response (Level 3, grade C).

### Renal amyloid

The most common renal manifestation of AL amyloidosis is the nephrotic syndrome. While the glomerular filtration rate may be preserved in early-stage disease, progressive tubular damage from uncontrolled proteinuria may eventually lead to end-stage kidney disease.

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 minimize proteinuria. Strict fluid and salt restriction, and control of blood pressure and serum cholesterol are also recommended. The increased risk of venous thromboembolism in the nephrotic syndrome should be carefully considered prior to the use of immunomodulatory agents (including thalidomide, lenalidomide and pomalidomide), which are known to potentiate venous thrombosis. Prophylactic anticoagulation should be considered on a case-by-case basis in patients with nephrotic syndrome treated with an immunomodulatory 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\(^\text{103}\). 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\(^\text{109}\).

### Recommendations

- The nephrotic syndrome should be managed supportively with diuretic therapy, salt and fluid restriction (Level 4, Grade C).
- The use of ACE inhibitors should be limited to patients who do not have significant cardiac or autonomic nervous system involvement (Level 4, Grade C).
- The risks and benefits of prophylactic anticoagulation in patients with nephrotic syndrome should be considered on an individual basis (Level 4, Grade C).
- Renal replacement therapy should be considered in patients with end-stage kidney
- Disease, taking into account age, severity of other organ involvement and fitness for chemotherapy (Level 3, Grade C).
- Renal transplantation may be considered on an individual basis (Level 3, Grade C).

**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 2.5mg tds during the day and titrated to a maximum dose of 10mg tds. Side-effects may include tachycardia, hypertension and restlessness. Fludrocortisone 100-200mcg/day is less effective and often poorly tolerated due to fluid retention.

**Recommendations**

- Patients with orthostatic hypotension should be screened for hypoadrenalism with the short Synacthen test (Level 4, Grade C).
- Support stockings are an inexpensive and safe intervention that may be effective (Level 4, Grade C).
- Midodrine can be used up to 30mg/day in divided doses (Level 4, Grade C).

**Gastrointestinal amyloid**

Amyloid infiltration of the gastrointestinal tract may be subclinical or may present with weight loss, malabsorption or GI bleeding. It is estimated that up to 25% of AL patients are malnourished, with one study finding that a baseline body mass index <22 and prealbumin <200mg/L represent adverse prognostic indicators. Identifying and addressing nutritional needs in these patients is difficult and it is recommended that input and follow-up from a specialist dietitian be offered to patients.

Motility disturbance including constipation and diarrhea may result from concomitant autonomic neuropathy. A hierarchical approach using oral antimitotility 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 diarrhea. Palliative end-ileostomy has also been reported.

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.
6. Conclusion

AL amyloidosis is a rare disorder for which the diagnosis and management has evolved considerably in the last decade. New prognostic assessment tools, particularly the cardiac biomarkers, and standardised haematological and organ response criteria have improved assessment of patients. New treatment options have allowed tailoring of treatment to individual patients and clinical trials are awaited to define the optimal therapy for newly diagnosed patients. The above treatment guidelines from the Australian Myeloma Scientific Advisory Group to the Myeloma Foundation of Australia are based on current published data and clinical experience. We hope these guidelines will assist Australian clinicians and improve the management of patients with AL amyloidosis.
### Appendix 1: Chemotherapy regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Reference</th>
<th>Chemotherapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan-based</td>
<td></td>
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<tr>
<td>MP</td>
<td>Kyle 1997[^22]</td>
<td>Melphalan 0.15 mg/kg po D1-7</td>
<td>Cycles repeated every 6 weeks for 2 years or until signs of serious toxicity. Due to low response rates, MP regimens are now superseded by M-Dex regimens.</td>
</tr>
<tr>
<td></td>
<td>Prednisone 0.8mg/kg po D1-7</td>
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<tr>
<td>M-Dex</td>
<td>Palladini 2004[^25]</td>
<td>Melphalan 0.22 mg/kg po D1-4</td>
<td>Cycles repeated every 28 days for up to 9 cycles in responders, or until 2 cycles beyond maximal response, progressive disease or serious toxicity. Median number of cycles = 5 (personal communication, Giovanni Palladini)</td>
</tr>
<tr>
<td></td>
<td>Jaccard 2007[^63]</td>
<td>Dexamethasone 40mg po D1-4</td>
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<tr>
<td></td>
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<td></td>
<td>Prophylactic omeprazole (20 mg/d), ciprofloxacin (250 mg twice daily), and itraconazole (100 mg/d) given D1-10.</td>
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<td></td>
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<td></td>
<td>The dose of melphalan was adjusted during the first three courses in order to induce mild mid-cycle leukopenia. Prophylaxis with proton-pump inhibitors and trimethoprim–sulfamethoxazole was recommended.</td>
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<tr>
<td>Mel200</td>
<td>Skinner 2004[^29]</td>
<td>Melphalan 2000mg/m^2 IV, 1-2 days prior to stem cell reinfusion</td>
<td>Mobilisation with G-CSF 10mcg/kg daily</td>
</tr>
<tr>
<td></td>
<td>Gertz 2010[^43]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jaccard 2007[^63]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide-based[^a]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTD</td>
<td>Wechalekar 2007[^75]</td>
<td>Cyclophosphamide 500mg po D1, 8, 15</td>
<td>Thalidomide maintenance therapy was only considered for responders and was decided on by a combination of patient preference and tolerance to treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thalidomide 100mg po D1-21</td>
<td>Dose attenuation did not affect haematologic response but significantly reduced grade ≥2 toxicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dexamethasone 40mg po D1-4, 9-12</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cycles repeated every 21 days until stable clonal response on consecutive samples at least 4 weeks apart.</td>
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<tr>
<td>CTDa</td>
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</tbody>
</table>

[^22]: Kyle 1997[^22]
[^63]: Jaccard 2007[^63]
[^29]: Skinner 2004[^29]
[^43]: Gertz 2010[^43]
[^75]: Wechalekar 2007[^75]
[^76]: CTDa
<table>
<thead>
<tr>
<th>Studies</th>
<th>Agents</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-week intervals as tolerated) Dexamethasone 20mg po D1-4, D15-18 Cycles repeated every 28 days until stable clonal response on consecutive samples at least 4 weeks apart.</td>
<td></td>
</tr>
<tr>
<td><strong>Lenalidomide-based</strong>**</td>
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<td></td>
</tr>
<tr>
<td>RD</td>
<td>Sanchorawala 2007</td>
<td>Lenalidomide 15 mg po D1-21 Dexamethasone 10-20 mg po D1-4, D9-12, D17-20 alternate cycles (if no HR by cycle 3) Cycles repeated every 28 days.</td>
</tr>
<tr>
<td>CRd</td>
<td>Kumar 2012</td>
<td>Cyclophosphamide 300mg/m² po D1, 8, 15 Lenalidomide 15mg po D1-21 Dexamethasone 40mg po D1, 8, 15, 22 Cycles repeated every 28 days for up to 24 cycles (with cessation of cyclophosphamide after cycle 12)</td>
</tr>
<tr>
<td>CRd</td>
<td>Kastritis 2012</td>
<td>Cyclophosphamide 100mg po D1-10 Lenalidomide 15mg po D1-21 Dexamethasone 20mg po D1-4 Cycles repeated every 28 days for a planned duration of 12 cycles.</td>
</tr>
<tr>
<td><strong>Bortezomib-based</strong>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vd</td>
<td>Kastritis 2010</td>
<td>Bortezomib 1.3mg/m² IV D1, 4, 8, 11 Dexamethasone 40mg po D1-4 Cycles repeated every 21 days.</td>
</tr>
<tr>
<td>CVD</td>
<td>Mikhail 2012</td>
<td>Bortezomib 1.5 mg/m² IV D1, 8, 15, 22 Cyclophosphamide 300mg/m² po D1, 8, 15 Dexamethasone 40mg po D1, 8, 15, 22 Cycles repeated every 28 days for a median of 3 cycles.</td>
</tr>
<tr>
<td>CVD</td>
<td>Venner 2012</td>
<td>Bortezomib 1.0 mg/m² IV D1, 4, 8, 11 (increased to 1.3 mg/m² if well tolerated) Cyclophosphamide 350 mg/m² po D1, 8, 15 Dexamethasone 20 mg po D1, 4, 8, 11 (increased to 20 mg for 2 days if well tolerated)</td>
</tr>
</tbody>
</table>
Cycles repeated every 21 days for up to 8 cycles.

| MDV Zonder 2009* | Melphalan 9 mg/m² PO D1-4 (6 mg/m² if Cr > 2.5 mg/dL)  
Bortezomib 1.3 mg/m² IV D1, 8, 15, 22 (1.0 mg/m² if PN at baseline)  
Dexamethasone 40 mg PO/IV days of & days after bortezomib (20 mg if >70 yrs, peripheral edema or heart failure) |

Cycles repeated every 4-6 weeks to a maximum of 20 cycles.

*Thalidomide is available for upfront treatment of multiple myeloma through the Pharmaceutical Benefit Scheme Highly Specialised Drug Program. Applications are made through Medicare Australia, please visit [http://www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)

**Lenalidomide as monotherapy or in combination with corticosteroid is available through the Pharmaceutical Benefit Scheme Highly Specialised Drug Program for patients with multiple myeloma who have progressive disease after at least 1 prior therapy, and who have undergone or are ineligible for a primary stem cell transplant. The patient must have experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease. Applications are made through Medicare Australia, please visit [http://www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)

***Bortezomib is available alone or in combination with chemotherapy through the Pharmaceutical Benefit Scheme Highly Specialised Drug Program for the treatment of multiple myeloma in a) newly diagnosed patients who are eligible for high-dose chemotherapy and autologous stem cell transplantation, b) newly diagnosed patients who are ineligible for high dose chemotherapy and autologous stem cell transplantation, c) newly diagnosed patients requiring or at risk of requiring dialysis for severe acute renal failure, d) patients with progressive disease who have undergone or are ineligible for high dose chemotherapy and autologous stem cell transplantation and have failed a trial of at least 4 weeks of thalidomide treatment at a dose of at least 100mg daily. Applications are made through Medicare Australia, please visit [http://www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)
Appendix 2: Contact details for specialised tests for amyloid diagnosis

Genetic screening
Australia:  Mutation analysis of ATTR, AFib, ApoA1, Alys
Associate Professor David Booth, Genetics of Multiple Sclerosis Research Group, Westmead Millenium Institute for Medical Research, Westmead NSW; david.booth@sydney.edu.au

New Zealand:  Mutation analysis of ATTR, AFib
Canterbury Health Laboratories, Christchurch, NZ

UK:  Mutation analysis of ATTR, AFib, ApoA1, ApoA2, Alys
Professor Philip Hawkins, National Amyloidosis Centre, London, UK; p.hawkins@ucl.ac.uk

Tandem Mass Spectrometry
Australia:  Dr Patricia Renaut, Dept of Anatomical Pathology, Princess Alexandra Hospital, Brisbane; Patricia_Renaut@health.qld.gov.au
New Zealand:  Dr Hugh Goodman, Haematology Dept, Waikato Hospital, Hamilton; Hugh.Goodman@waikatodhb.health.nz

SAP scintigraphy
UK:  Professor Philip Hawkins, National Amyloidosis Centre, London, UK; p.hawkins@ucl.ac.uk
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in
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is
associated
with
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clonal
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of
survival
using
cardiac
troponins
and
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troponins
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who
present
with
dominant
neuropathy.

predicts
survival
in
primary
systemic
amyloidosis.

novel
prognostic
factor
in
primary
systemic
amyloidosis.

survival
and
response
after
high
with
newly
diagnosed
systemic
light
chain
amyloidosis
and
seve
intravenous
melphalan
dexamethasone
is
not
able
to
overcome
the
poor
prognosis
of
patients
t(11;14)
and
survival
of
patients
with
light
chain
(AL)
amyloidosis.

pathophysiology
and
clinical
features
of
disease
are
linked
to
clonal
total
plasma
cell
expression
of
cyclin
D1
in
systemic
light-chain
amyloidosis.

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with
intravenous
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is
not
able
to
overcome
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patients
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and
N-terminal
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natriuretic
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a
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system
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of
survival
using
cardiac
troponins
and
N-terminal
pro-brain
natriuretic
peptide
in
patients
with
primary
systemic
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undergoing
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