

AL amyloidosis: Singapore Myeloma Study Group consensus guidelines on diagnosis, treatment and management

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ABSTRACT

AL amyloidosis is the most common form of systemic amyloidosis. However, the non-specific nature of presenting symptoms requires the need for a heightened clinical suspicion to detect unexplained manifestations in the appropriate clinical setting. Early detection and treatment are crucial as the degree of cardiac involvement emerges as a primary prognostic predictor of survival in a patient with AL amyloidosis.

Following the diagnosis of AL amyloidosis with appropriate tissue biopsies, prompt treatment with a bortezomib, cyclophosphamide and dexamethasone-based first-line induction with or without daratumumab should be initiated. The goal of treatment is to achieve the best haematologic response possible, ideally with involved free light chain <20 mg/L, as it offers the best chance of organ function improvement.

Treatment should be changed if patients do not achieve a partial response within 2 cycles of treatment or very good partial response after 4 cycles or after autologous stem cell transplant, as achievement of profound and prolonged clonal responses translates to better organ response and long-term outcomes. Early involvement of multidisciplinary subspecialists such as renal physicians, cardiologists, neurologists, and gastroenterologists for optimal maintenance and support of involved organs is recommended for optimal management of patients with AL amyloidosis.

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CLINICAL IMPACT

What is New

- First in Asia guideline highlighting the diagnosis, treatment and management of AL amyloidosis.
- The goal of treatment should be to achieve the best hematologic response rapidly as it offers the best chance of organ function improvement.

Clinical implications

- Early diagnosis, tailored treatment strategies to achieve profound and rapid involved light chain responses, and collaboration among specialists is key in managing AL amyloidosis effectively.

Amyloidosis refers to disorders characterised by the deposition of insoluble amyloid fibrils, which are pathogenic,¹ resulting in organ dysfunction. Amyloidoses differ in the protein precursor undergoing aggregation and downstream target organs implicated. Consequently, clinical manifestations are varied, from localised amyloidosis in Alzheimer's disease, to systemic amyloidosis such as immunoglobulin light chain amyloidosis (AL), reactive amyloidosis (AA) and transthyretin amyloidosis (ATTR). The most common form of systemic amyloidosis is amyloid fibrils derived from immunoglobulin light chains, designated as AL amyloidosis, produced by underlying neoplastic plasma cells or B-cell clones.

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In this guideline, we will focus on AL amyloidosis. These guidelines are developed as a consensus by the Singapore Myeloma Study Group (MSG) to provide evidence-based recommendations for diagnosing and managing AL amyloidosis in the local Singapore context. The recommendations are not intended to be prescriptive and should be used with sound clinical judgment by haematologists and other relevant specialists with experience in managing patients with AL amyloidosis.

The following topics will be outlined: (1) epidemiology and pathophysiology; (2) diagnosis, staging and risk stratification; (3) treatment; (4) supportive care; and (5) drug toxicity and dose adjustments.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Epidemiology

The epidemiology of AL amyloidosis has not been well characterised as it is a rare disease. Incidence has remained stable, with 9.7–14.0 cases per million person-years.² A similar population-based cohort study in Taiwan showed that the crude annual incidence of AL amyloidosis was 8.46 per million in 2016 and 8.31 per million population in 2019.³ However, prevalence has increased, and in a population-based study in the US, the prevalence of AL amyloidosis was 15.5 cases per million in 2007 and 40.5 in 2015.² This increase is likely due to a significant improvement in overall survival over time.

The mean age of AL amyloidosis in patients is approximately 63 years, doubling in individuals >65 years compared with those aged 35–54 years.⁴

Pathophysiology

Disorganisation of normal protein structure leads to abnormal interactions, which can result in disease. The amyloid fibrils in AL amyloidosis are composed of misfolded immunoglobulin light chains that form proteolysis-resistant beta-pleated sheets, resulting in extracellular deposition of amyloid and end-organ impairment. Immunoglobulin light chains can be produced by atypical clonal B lymphocytes or more commonly, clonal plasma cells. Somatic mutations of the variable chain of such a clonally produced free light chain and disruption of homeostasis of the naturally existent chaperone pathways responsible for the metabolism of such extracellular proteins are often the key pathogenetic mechanisms.⁶

As such, underlying plasma cell dyscrasia is often the precursor for AL amyloidosis. The relative risk of AL amyloidosis is 8.8 in patients with monoclonal gammopathy of undetermined significance (MGUS) compared with those without. In 5–7% of patients with AL amyloidosis, an IgM-

producing clone with MGUS or Waldenstrom's macroglobulinemia characteristics is responsible for the pathology. Rarely, AL amyloidosis is associated with non-lymphoplasmacytic lymphoproliferative disorders such as marginal zone lymphoma and chronic lymphocytic leukemia.⁷

The material that constitutes the deposits determines the properties and behaviours and consequently, the manifestations of amyloid disease. The critical concentration required for nucleation and formation of deposits varies depending on the stability of light chains. The accumulation of amyloid deposits in parenchymal tissue leads to cumulative tissue damage, which results in organ dysfunction and eventually, organ failure.⁸ Therefore, early diagnosis of AL amyloidosis and administration of effective therapy that can produce a rapid and profound reduction of the amyloid precursors are critical to stop fibril growth and disease progression. Amyloid deposits are generally resistant to degradation, but slow natural clearance of amyloid deposits by endogenous chaperone pathways can occur.

DIAGNOSIS, STAGING AND RISK STRATIFICATION

For the optimal treatment of AL amyloidosis, the initial evaluation must be comprehensive. Confirmation of diagnosis, establishing the extent, sites and severity of disease involvement and its clinical consequences, as well as detailed assessment of any potential co-morbidities likely to affect treatment choices, are essential before commencing treatment.

Clinical manifestations

The clinical presentation of AL amyloidosis depends on the number and nature of the organs affected. Most patients have 2 or more organs involved at diagnosis, but about a third have only 1 organ affected.⁹ The diagnosis of systemic AL amyloidosis is often delayed as initial symptoms may be non-specific (e.g. fatigue/unintentional weight loss, with the median time from symptom onset to diagnosis being 6–10 months.¹⁰ The incidence, symptoms of organ involvement, diagnostic findings and consensus criteria for determining organ involvement by AL amyloidosis are highlighted in Table 1. As the presenting symptoms are often related to end-organ dysfunction in this multisystem disease, and advanced amyloidosis carries a high risk of mortality even with treatment, a high index of suspicion to investigate an unexplained manifestation in the appropriate clinical setting can lead to an early diagnosis of AL amyloidosis and ultimately lead to improvement of overall survival of patients.

Some examples of such clinical scenarios are patients with unexplained diastolic cardiac dysfunction, heart failure with preserved ejection fraction, especially with disproportionately higher N-terminal pro-brain natriuretic peptide (NT-proBNP) values, or patients requiring incrementally reduced anti-hypertensives due to pseudo “normalisation” of blood pressure caused by visceral neuropathy. Hepatomegaly with or without splenomegaly and associated elevated alkaline phosphatase is a common presentation to gastroenterologists and general physicians. Screening for serum free light chains (FLC) by nephrologists in patients with proteinuria and diabetes where blood sugars have been well-controlled can also assist in the early diagnosis of AL amyloidosis. Although periorbital purpura and macroglossia are pathognomonic symptoms of AL amyloidosis, it only occurs in 10–15% of patients.¹¹

Patients being followed up for MGUS or smouldering multiple myeloma (SMM) need to be assessed for clinical features of AL amyloidosis and investigated appropriately while also being monitored for disease progression to multiple myeloma (MM).

Suspicion of amyloidosis often starts with a consistent clinical syndrome, imaging findings suspicious of amyloidosis (e.g. on echocardiogram), or rarely an incidental tissue biopsy with amyloid deposit. Potential clinical scenarios that should raise a suspicion of amyloidosis are discussed and presented in Table 1.^{12–14}

Occasionally, a diagnosis of amyloidosis on tissue biopsy might be noted incidentally where there has not been a clinical suspicion of amyloid disease. Careful work-up of such patients is required as localised forms of AL amyloidosis have been recognised. This includes localised AL amyloidosis, in which light chain deposits are localised to only skin, upper aerodigestive tract, genitourinary tract or soft tissues without any evidence of a monoclonal protein in either serum, urine or clonal plasma cells in the bone marrow. Localised AL amyloidosis is thought to arise from the FLC production by polyclonal plasma cells in the affected area. Recognition of this entity is essential since its treatment involves either observation, surgery or local radiotherapy rather than systemic chemotherapy.¹²

Approach to diagnosis and confirmation of sub-type

The diagnosis of AL amyloidosis requires the following: (1) presence of a clinical syndrome consistent with amyloidosis; (2) tissue biopsy with histological confirmation of amyloid deposits; (3) evidence of monoclonal LC restriction by amyloid

typing of the tissue; and (4) presence of an underlying monoclonal plasma cell disorder (of the same isotype).

In circumstances where clinical suspicion of amyloidosis is raised, a proposed algorithm for the patient's work-up is outlined in Fig. 1.

Given that the diagnostic work-up can be time and resource-consuming and expensive, the extent of these investigations should be decided on the merit of the individual patient's clinical presentation by an experienced haematologist, carefully balancing the possible benefits of an early diagnosis and the consequences of delaying or missing a potential diagnosis of AL amyloidosis in discussion with other relevant specialities and taking the patient's perspectives into account.

The first diagnostic step is checking serum and urine immunofixation, protein electrophoresis and serum FLC assay. This comprehensive panel can identify >95% of AL amyloidosis patients.¹⁰ If the above shows a clear presence of monoclonal protein or FLC, bone marrow aspiration and biopsy are the next essential steps to confirm the presence of monoclonal plasma cells or B lymphocytes to quantify them by morphology, flow cytometry and trephine biopsy. Additionally, trephine biopsy is a surrogate site to demonstrate tissue amyloid deposits by Congo red staining. Unlike in MM, the median clone size of plasma cells in bone marrow is relatively low at <10%¹⁶. Hence, a good-quality aspirate and biopsy are crucial to positively identify a clonal population of plasma cells. In a patient with AL amyloidosis, if plasma cells are >10% (or with any CRAB features, i.e. hypercalcaemia, renal dysfunction, anaemia and destructive bone lesions; or MM defining events as per International Myeloma Working Group's definition), additional imaging (low-dose computed tomography [CT] or positron emission tomography-CT) must be performed to confirm that it is not secondary AL amyloidosis with concurrent MM. The prognosis of such patients is worse and more like MM, and should be managed as per the myeloma treatment paradigm. Bone marrow also allows for prognostication using fluorescence in situ hybridisation (FISH)-based cytogenetic evaluation of clonal plasma cells. Genomic prognostication in AL amyloidosis differs from that of MM, with markers considered good prognosis in MM having relatively poor outcomes in AL amyloidosis.

If a monoclonal protein and their source in terms of clonal plasma cells or lymphocytes in bone marrow are confirmed, the next step would be to confirm the presence of amyloid deposits with a tissue biopsy. Depending on the clinical situation, these interventions are performed concurrently to avoid time delay and allow prompt therapy initiation.

Table 1. Most common presenting symptoms/signs, incidence, diagnostic findings and consensus criteria of AL amyloidosis depending on organ involvement.¹³

Organ	Incidence (%)	Clinical manifestations	Investigations and diagnostic findings	Consensus criteria for involvement ^{14,15}
Heart	60–75	Exertional dyspnoea Orthopnoea Paroxysmal nocturnal dyspnoea Lower limb oedema Pleural effusions Arrhythmias	ECG - Disproportional QRS voltage to the degree of LV hypertrophy on imaging, conduction system disease, atrial fibrillation, pseudo infarct pattern TTE - LV hypertrophy (mean left ventricular wall thickness >12 mm), thickened valves and interatrial septum - Diastolic dysfunction with preserved LVEF, reduced GLS/apical sparing pattern on GLS, increased RV wall thickness MRI - Subendocardial late gadolinium enhancement; elevated ECV/T1; abnormal myocardial nulling	- Mean left ventricular wall thickness on echocardiography >12 mm, no other cause found - NT-proBNP >39 pmol/L in the absence of renal failure or atrial fibrillation
Kidney	50–70	Lower limb oedema Anasarca Uraemia	Proteinuria, typically nephrotic range Acute kidney injury Hypercholesterolaemia Hypothyroidism Hypercoagulability	24-hr urine protein >0.5 g/day, predominantly albumin
Liver	20	Right upper quadrant tenderness Early satiety Weight loss	Hepatomegaly Isolated increase in alkaline phosphatase Coagulopathy due to coagulation factor deficiency ^a	- Hepatomegaly with total liver span >15 cm in the absence of heart failure, or - Alkaline phosphatase >1.5 times upper limit of normal
Gastrointestinal tract	10	Diarrhoea Weight loss Malabsorption Hematochezia or melena		Positive biopsy with interstitial involvement
Lung	30–90	Shortness of breath Dry cough Recurrent pleural effusions	Pleural effusions Interstitial pulmonary nodules	- Direct biopsy verification with symptoms, or - Radiographic pattern of interstitial infiltration
Peripheral nervous system	10–20	Dysaesthesia Paraesthesia Sensory loss	EMG Symmetric, axonal sensorimotor PN	Clinical findings

Table 1. Most common presenting symptoms/signs, incidence, diagnostic findings and consensus criteria of AL amyloidosis depending on organ involvement.¹³ (Cont'd)

Organ	Incidence (%)	Clinical manifestations	Investigations and diagnostic findings	Consensus criteria for involvement ^{14,15}
Autonomic nervous system	10–20	Orthostatic hypotension Early satiety Intestinal dysmotility (gastric-emptying disorder, pseudo-obstruction) Erectile dysfunction Voiding dysfunction	Delayed gastric emptying Positive tilt test	Clinical findings
Soft tissue	10–20	Periorbital or upper body purpura Macroglossia Submandibular swelling Skeletal muscle pseudohypertrophy Arthropathy Myopathy Ecchymotic bullae Jaw or buttock claudication (vascular amyloid) Carpal tunnel		Clinical findings

ECG: electrocardiogram; ECV: extracellular volume; EMG: electromyography; GLS: global longitudinal strain; LV: left ventricular; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-brain natriuretic peptide; PN: peripheral neuropathy; RHC: right heart catheterisation; TTE: transthoracic echocardiogram.
^a Factor X deficiency can occur independently of liver involvement owing to the direct absorption of factor X by amyloid fibrils.

The biopsied tissue should demonstrate positive staining with Congo red by standard light microscopy and a characteristic apple-green birefringence by polarised light. The sensitivities of biopsy of the bone marrow, fat pad and rectal biopsies are 63%, 73%, and 69–97%, respectively, while biopsy of kidney, liver or cardiac tissue has a sensitivity of 87–98%.¹⁷ Despite the higher sensitivity of biopsies from the liver, heart and kidneys, these have a higher bleeding risk. Therefore, sites such as bone marrow, fat pad and rectal biopsies are often preferred initial sites for biopsy. Careful attention to the patient's bleeding history or bleeding symptoms and signs, if any; and evaluation of platelet counts, a clotting screen with activated partial thromboplastin time (aPTT), prothrombin time (PT) and if indicated, additional factor levels (e.g. Factor X) are all essential before any biopsies are planned as several coagulation defects can be associated with AL amyloidosis. If there are bleeding symptoms or abnormal clotting results, patients need to be carefully managed with haemostatic and/or blood products to reverse them before a biopsy can be performed safely. It cannot be overemphasised that all steps to avoid catastrophic peri-procedural bleeding needs to be taken (e.g. choice of least risky biopsy site, correction of coagulation abnormalities, platelet transfusions, anticoagulation withdrawal, etc.) before the diagnostic procedure.

It is important to note that in the bone marrow biopsy, amyloid deposition within the stroma, as opposed to periosteal or vessel wall, is more suggestive of a diagnosis of systemic AL amyloidosis since AA or TTR-type amyloid could be seen in these latter locations. Hence, if Congo red-positive amyloid is noted only in the periosteal region or within the vessel wall in the marrow, it should warrant at least a concurrent fat pad biopsy to improve the specificity. Subcutaneous fat combined with bone marrow biopsy can diagnose approximately 90% of patients.¹⁸ If the bone marrow and fat pad biopsy are negative, but the clinical suspicion remains high, a biopsy of end organs, especially the involved organ (e.g. kidney, peripheral nerve, liver, cardiac, etc.), is necessary for diagnosis.

The next step is to prove that the identified amyloid deposits are derived from monoclonal light chains. Mass spectrometry is the gold standard for characterising amyloid type with nearly 100% sensitivity and specificity.¹⁹ Ideally, Congo red positivity should be subjected to mass spectrometric confirmation. However, since it is not available in Singapore and can be expensive to perform, we suggest that it is left to the

discretion of treating individual physicians to pursue this based on the given clinical situation. Alternative typing methods that are available in Singapore include immunofluorescence and immunohistochemistry, which are particularly sensitive in kidney biopsies. The main limitation of these antigen-antibody-based assays is suboptimal sensitivity of 42–96%.²⁰ Electron microscopic studies can also differentiate light-chain amyloidosis from non-amyloid immunoglobulin deposition diseases.

It is paramount that tissue subtyping is accurate, as the presence of monoclonal protein or abnormal light chain ratio in a patient with amyloidosis does not prove that the amyloidosis is of the AL subtype. It is increasingly recognised that MGUS can co-exist with senile amyloidosis (ATTRw) in up to 23% of cases, as well as other forms of amyloidosis, including hereditary forms.²¹

Staging and prognostication of AL amyloidosis

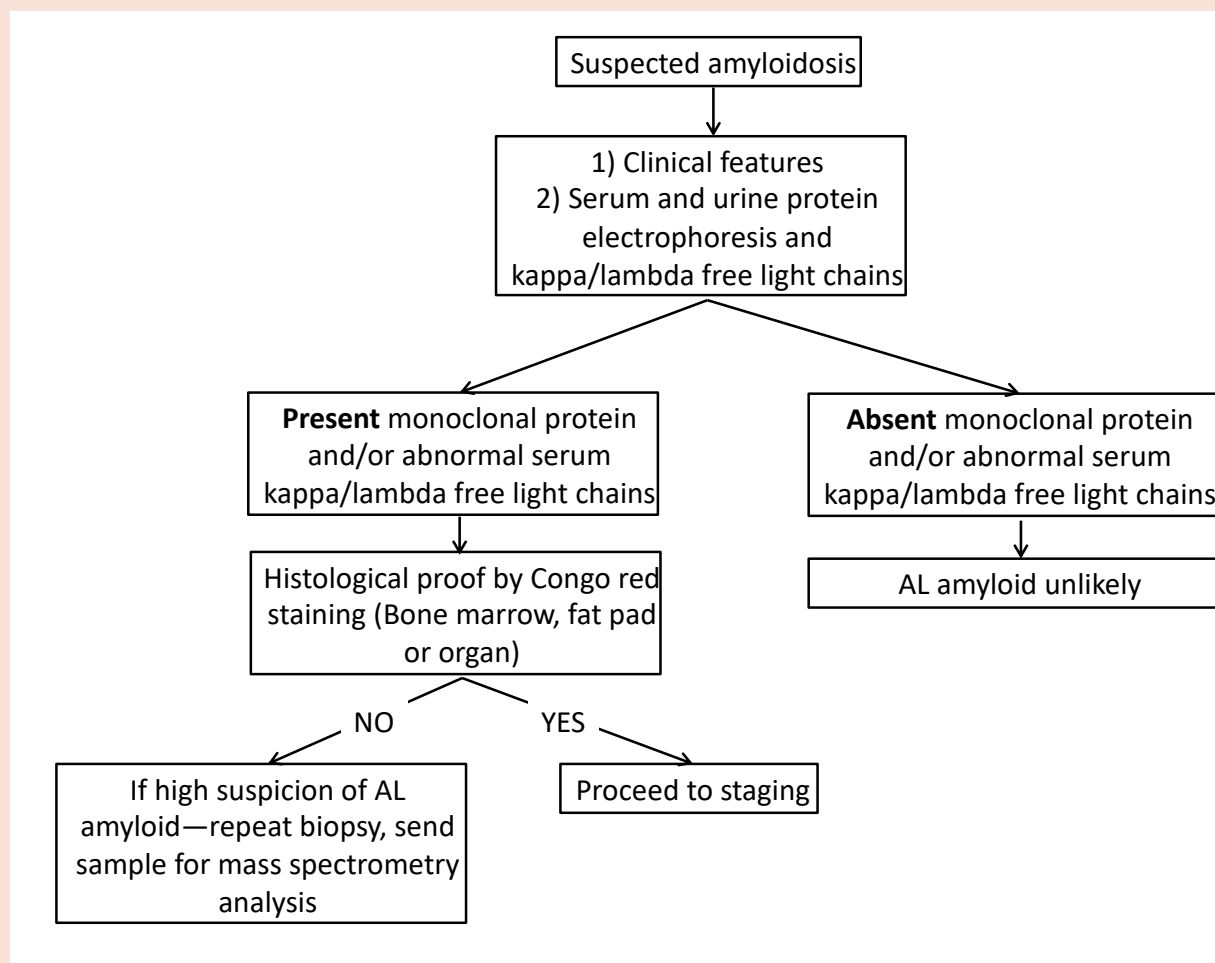
Once the diagnosis of AL amyloidosis has been established, further investigations are required to evaluate the underlying organ involvement, as outlined in Table 2.

The parameters used for staging and prognostication of AL amyloidosis include serum kappa lambda FLC and protein electrophoresis with immunofixation, and bone marrow plasma cells (BMPC) and FISH genetics.

With serum kappa lambda FLC and protein electrophoresis with immunofixation, a difference between the involved and uninvolved FLC (dFLC) of ≥ 50 mg/L at diagnosis has been defined as necessary for using changes in dFLC as a disease marker for monitoring treatment response²² and prognostication as outlined in the next section. This includes about 85% of patients with newly diagnosed systemic AL amyloidosis. For 15% of patients with minimally abnormal FLC, monitoring the haematological response relies on a measurable monoclonal protein, defined as >5 g/L.²² A minority of patients lack a good measurable marker of haematological response.

With BMPC and FISH genetics, a higher plasma cell burden has been correlated with a worse prognosis. A study by Muchtar et al. showed that survival was inversely associated with BMPC, with median overall survival being 81, 33 and 12 months for $<5\%$, $5\text{--}19\%$ and $\geq 20\%$ BMPC, respectively, $P < 0.001$, independent of cardiac risk category or stem cell transplant eligibility.²³ The presence of t(11;14) versus the absence of t(11;14) was associated with inferior haematologic median event-free survival (3.4 vs 8.8 months $P = 0.002$), median overall survival (8.7

Fig. 1. Diagnostic algorithm for suspected amyloidosis.



vs 40.7 months) and remission rate (³ very good partial response [VGPR] 23% vs 47% $P=0.02$) in a cohort of patients treated with bortezomib, cyclophosphamide and dexamethasone (VCD).^{24,25}

Once the diagnosis of AL amyloidosis has been established, further investigations are required to evaluate the underlying organ involvement, as outlined in Table 2.

Cardiac staging and prognosis

The prognosis of AL amyloidosis is dependent on the underlying plasma cell clone and the extent of organ involvement. Survival has improved in the last few decades, but the proportion of patients dying within the first 6 to 12 months of diagnosis remains significant, at approximately 25%.²⁶

The degree of cardiac involvement is the single most important predictor of short-term and long-term survival. This led to the development of prognostic models, with Mayo 2004 being the

initial model developed to stratify patients into 3 prognostic groups based on troponin T and NT-proBNP values.²⁷ The subsequent European collaboration modification (Mayo 2004 with European modification) further risk-stratified the high-risk subgroups based on NT-proBNP levels. It was deemed the best in identifying patients with the highest risk of early death. Subsequently, the Mayo 2012 model incorporating dFLC at diagnosis was shown to have a better discriminating ability to identify patients with different outcomes from among the previous stage groups 3 years after diagnosis.²⁸ A later model by Boston University using troponin I and BNP allows centres without access to NT-proBNP to utilise the model²⁹ (Table 3).

Renal staging and prognosis

Renal staging models help predict the risk of dialysis dependence in patients. For example, the 3-stage model based on estimated glomerular filtration rate

Table 2. Investigations for patients with AL amyloidosis.

Group of patients	Investigations
All patients	Full blood count Renal (kidney) panel 24-hour urine protein or spot urine protein/creatinine ratio Serum calcium Liver panel Fasting blood sugar + HbA1C Haemetinics—iron panel/vitamin B12/folate (as required) Serum troponin T/high-sensitivity troponins Serum NT-proBNP ECG PT/aPTT (factor levels if indicated)
Cardiac involvement — signs and symptoms	Transthoracic echocardiogram Cardiac MRI
Neuropathy/autonomic symptoms	Nerve conduction study Autonomic function tests
Lung	Chest X-ray Lung function
Suspicion of myeloma	Bone investigation, e.g. PET-CT

aPTT: activated partial thromboplastin time; ECG: electrocardiogram; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography; PT: prothrombin time; HbA1C: haemoglobin A1C; NT-proBNP: N-terminal pro-brain natriuretic peptide

Table 3. A) Cardiac risk stratification models for AL amyloidosis, B) Median overall survival, based on respective risk stratification models.

A. Cardiac risk stratification models for AL amyloidosis				
Source	hsTnT (pg/mL)/cTnI (ug/L)	NT-proBNP (ng/L)	dFLC (mg/L)	BNP (pg/mL)
Mayo 2004	>54/>0.1 (1 point)	>332 (1 point)		
Mayo 2004 with European modification	>54/>0.1 (1 point)	>332 (1 point) > 8500 (2 points)		
Mayo 2012	>54/>0.1 (1 point)	>1800 (1 point)	>180 (1 point)	
Boston University 2019	NA />0.1 (1 point)			>81 (1 point) >700 (2 points)

Thresholds for biomarkers are reported based on the proposed modification of the staging systems²⁹

B. Stages with corresponding median overall survival (months)				
Source	Stage 1 (0 points)	Stage 2 (1 point)	Stage 3a (2 points)	Stage 3b (or Stage 4 in Mayo 2012) (3 points)
Mayo 2004	130	54		10 (stage 3)
Mayo 2004 with European modification	130	54	24	4
Mayo 2012	130	72	24	6
Boston University 2019	NR	9.4	4.3	1

BNP: brain natriuretic peptide; CTnI: cardiac troponin I; dFLC: difference between involved and uninvolved free light chain; hsTnT: high-sensitivity cardiac troponin; NR: not reached; NT-proBNP: N-terminal pro-brain natriuretic peptide

The median overall survivals are derived from application of the established staging systems to a more contemporary cohort⁸⁸

(eGFR) and proteinuria was able to dichotomise patients into low vs high-risk of progression to dialysis as outlined in Table 4.³⁰

Table 4. Renal risk stratification.

1 point each for:
1) eGFR <50 mL/min per 1.73m ²
2) urine protein >5 g/24h
3-year risk of dialysis dependence (%)
Renal stage I (0 point): 4
Renal stage II (1 points): 30
Renal stage III (2 points): 85

TREATMENT

Goals of treatment

Summary

- The goal of treatment should be to achieve the best haematologic response possible for a given patient (involved free light chain [iFLC] <20 mg/L where feasible), as it offers the best chance of organ function improvement. However, this must be weighed against treatment-related toxicity and the limitations of the assays.
- Patients who do not achieve at least partial response (PR) within 2 cycles of treatment commencement or VGPR after 4 cycles or after autologous stem cell transplant (ASCT) should be considered for alternative therapy.
- Achievement of profound and prolonged clonal responses, which translates into better organ responses, should be the long-term goal of therapy.
- Early involvement of multidisciplinary subspecialists such as renal physicians, cardiologists, neurologists and gastroenterologists for optimal maintenance and support of involved organs is recommended.

Treatment of localised AL amyloidosis (e.g. tracheobronchial, lung, breast) is guided by the severity of the patient's symptoms and usually consists of local resection or, in select cases, local radiotherapy.³¹ The overall recurrence rate of localised amyloidosis is approximately 20%, up to 50% for urothelial,³² laryngeal³³ and tracheobronchial amyloidosis.³⁴ Chemotherapy is inappropriate in these forms as the deposits come from polyclonal plasma cells and are to be avoided.

Virtually all patients with systemic amyloidosis require treatment, except for localised amyloidosis and patients with MGUS or SMM with incidental

amyloid deposits in the bone marrow without any evidence of organ involvement. Treatment of systemic AL amyloidosis is targeted at eliminating the plasma cell clone. In the past, therapy has primarily been directed at reducing precursor FLC production, limiting further organ damage, and allowing time for endogenous resorption of tissue amyloid deposits. However, with the advent of effective novel agent therapy resulting in reduced early mortality and improved patient selection, the focus has shifted to achieving more profound and sustained clonal responses, which appear to result in better organ function recovery. Accordingly, we recommend that the overall aim of treatment should be to achieve at least VGPR or better, with iFLC <20 mg/L as the optimal response. Early and profound reductions in FLC concentrations are associated with the greatest chance of organ recovery (Table 5) and downstream prolongation of progression-free survival (PFS) and overall survival (OS).

While attaining complete remission (CR) is the goal of therapy, recent studies have shown that iFLC <20 mg/L or the dFLC <10 mg/L is correlated with improved outcomes. A few studies have shown that patients who achieved a VGPR or better and with iFLC <20 mg/L had superior organ response (OR), PFS, and OS compared with levels >20 mg/L.³⁵⁻³⁶ In a Mayo study, iFLC normalisation was not shown to predict organ response or survival, supporting the data that iFLC should be reduced as low as possible for the best outcomes, preferably to <20 mg/L.³⁶

However, in patients with renal impairment or ongoing infection or inflammation, it is often impossible to discern if the elevation of iFLC is monoclonal or polyclonal. In these cases, repeat testing is advised, and if still inconclusive, a bone marrow assessment may be required to determine if there are residual clonal plasma cells.³⁶

In addition to deep haematologic response (HR), rapid attainment of HR has portended a more favourable outcome. Studies have shown that rapid HR within 1 month translated into a survival benefit at 12 months,³⁸ suggesting that ongoing light chain toxicity is a critical factor in end-organ damage and is potentially reversible with early HR. Therefore, the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) consensus statement 2020 has recommended that patients who do not achieve at least partial response within 2 cycles or VGPR within 4 cycles of therapy or after ASCT should be considered for alternative therapy.³⁹

Minimal residual disease (MRD) assessment in AL amyloidosis has also been prognostic for PFS and OS. A study by the Mayo group recently

showed that MRD negativity was more likely to be achieved among patients who received ASCT and were in CR. MRD negativity to a sensitivity of 10^{-5} in patients who achieved CR was associated with a higher likelihood of cardiac response and improved 12-month PFS.⁴⁰ However, both prognostic evaluation and treatment decisions based on MRD values are currently underway in clinical studies, and these results will inform future practice. Hence, in the global context, MRD in AL amyloidosis remains a research tool, and we recommend against the routine use of this tool in clinical practice to guide treatment decisions at this point.

Put together, the likelihood of OR is contingent on achieving deep and rapid HR, with OR lagging behind HR. The median time from first-line treatment in the pre-novel agent era to heart, kidney and liver response was 9, 6 and 6 months, respectively, with the median time to best organ responses at 24, 29 and 35 months, respectively.⁴¹

Treatment options

Accurate risk stratification, as outlined above, is crucial in deciding the treatment strategy. Approximately 20–30% of newly diagnosed patients are candidates for ASCT, and more may be eligible after effective upfront therapy with organ recovery.⁴²

Due to the rarity of AL amyloidosis, there is a paucity of large-scale randomised control trials to inform therapy. As such, enrolment into clinical trials should be considered if available.

Frontline therapy

Summary

- Recommended first-line induction is with combination chemotherapy; bortezomib cyclophosphamide and dexamethasone with or without daratumumab (Fig. 2).
- If the initial therapy is with VCD, patients with a suboptimal response (<VGPR) after 2 cycles can be considered for the addition of daratumumab to deepen the response.
- The duration of induction therapy is 4 to 6 cycles in patients with no co-existing MM or high-risk FISH abnormalities.
- Treatment response parameters (i.e. hazard ratio [HR] and odds ratio [OR]) must be evaluated after every cycle of chemotherapy.

Bortezomib

In the absence of large-scale randomised clinical trials, bortezomib-based therapy has been the

standard of care for treating newly diagnosed AL amyloidosis in the last decade, primarily based on single-centre prospective or large retrospective cohort studies. The addition of bortezomib has been shown to improve outcomes. It is likely due to the increased sensitivity of plasma cells in AL amyloidosis to proteasome inhibition due to toxic light-chain-induced cellular stress.⁴³ A randomised phase 3 trial comparing bortezomib melphalan dexamethasone (VMD) vs melphalan dexamethasone (MD) showed that the addition of bortezomib-induced higher HR and VGPR/CR rates (79% vs 52%, VGPR/CR 64% vs 39%) and prolonged PFS and OS as compared to the MD arm (median OS not reached vs 34 months). There was no significant difference in the cardiac and renal response at 9 months after treatment initiation in both arms (cardiac response 38% vs 28%, renal response 44% vs 43%). The overall quality of life was also not affected by the addition of bortezomib.⁴⁴

One of the largest studies examining the use of bortezomib in the frontline setting is a prospective trial from a UK group,⁴⁵ which examined 915 patients. In this study, a majority of patients were treated with frontline VCD (94%) without the use of ASCT. Haematologic response rates were high, with objective response rate (ORR) of 65% and 49% achieving VGPR/CR. In patients with end-organ involvement, cardiac, kidney and liver response at 12 months were seen in 32.5%, 15.4% and 30%, respectively. Overall median survival in this cohort was 72 months. The median time to next treatment as not reached in patients who achieved dFLC responses of <10 mg/L, approaching outcomes reported with upfront ASCT. However, mortality in stage 3 patients was 40% within 6 months of diagnosis.⁴⁵ Therefore, findings support that bortezomib therapy improves long-term outcomes in AL but does not negate the risk of early mortality in AL amyloidosis, especially among patients in advanced stages. With a once-weekly dose, bortezomib has acceptable tolerability and safety profile, with the main side effect being peripheral neuropathy.⁴⁶ VCD is the preferred pre-ASCT regime, as melphalan is generally avoided before stem cell collection and ASCT.

Daratumumab

Daratumumab is a CD38-directed monoclonal antibody that has been demonstrated to have potent plasma cell-directed killing with deep remissions and prolonged PFS and OS in relapsed refractory and frontline treatment of multiple myeloma in combination with other anti-myeloma agents.

Table 5. A–D) Haematologic response and organ response criteria CIBMTR).*

(A) Haematologic response				
	Serum and urine immunofixation	serum FLC ratio	dFLC	
CR *requires all	Negative	Normal		
VGPR	-	-	<40 mg/L	
PR *requires any			>50% reduction (if >10 mg/dL or >100 mg/L at baseline)	
NR/SD	Does not meet criteria			
PD *requires any	• If progressing from CR, any detectable monoclonal protein or abnormal FLC ratio (light chain must double) • If progressive from PR/SD, ≥ 50% increase in the serum M protein to > 5 g/L, or ≥ 50% increase in urine M protein to > 200 mg/day • Serum FLC increase of ≥ 50% to > 100 mg/L			
(B) Cardiac response				
	NT-proBNP**	NYHA	cardiac troponin	EF
Cardiac response *Requires any	> 30% and > 300 ng /L decrease (if baseline ≥ 650 ng/L)	≥ 2 class decrease (if baseline class 3/4)		
NR/SD	Does not meet criteria	Does not meet criteria	Does not meet criteria	Does not meet criteria
PD *Requires any	> 30% and > 300 ng/L increase		≥ 33% increase	≥ 10% decrease
* CIBMTR amyloidosis response criteria https://www.manula.com/manuals/cibmtr/fim/1/en/topic/amyloidosis-response-criteria ** Recipients with progressively worsening renal function cannot be score for NT-proBNP progression. Progressively worsening renal function is defined as a 50% increase (at least 1g/day) of 24-hour urine protein from baseline to > 1g/day or a 25% worsening of serum creatinine or creatinine clearance from baseline				
(C) Hepatic response				
	Liver size		ALP	
Hepatic response *Requires all	≥ 2 cm decrease (If baseline (liver > 15 cm)		≥ 50% decrease	
NR/SD	Does not meet criteria		Does not meet criteria	
PD			≥ 50% increase	
(D) Renal response				
	24h urine protein		eGFR	
Renal response *Requires all	≥ 50% decrease of at least 0.5 g/24h (baseline > 0.5 g/24h)		< 25% decrease	
NR/SD	Does not meet criteria		Does not meet criteria	
PD *Requires any	≥ 50% increase of at least 1 g/24h to > 1g/24h		≥ 25% decrease	

ALP: alkaline phosphatase; CR: complete response; eGFR: estimated glomerular filtration rate; FLC: free light chain; dFLC: difference between involved and uninvolved free light chain; NR: no response; NYHA: New York Heart Association; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response

The ANDROMEDA study⁴⁷ is the largest Phase III randomised control trial for AL amyloidosis, where subcutaneous daratumumab given in combination with VCd was compared to VCd. Patients were allowed to have ASCT based on the country or local investigator's preference. VCd was given for 6 cycles in each arm, with patients in the daratumumab arm receiving daratumumab on a standard schedule (weekly for the first 2 cycles, every 2 weeks in cycles 3 to 6, and every 4 weeks thereafter) for up to a total of 24 cycles.

The primary endpoint was the overall rate of haematologic complete response (CR), defined as the normalisation of FLC levels, FLC ratio, and negative serum and urine immunofixation. The secondary endpoints were major organ deterioration-PFS, major organ deterioration-EFS (event-free survival), organ response rate, time to haematologic response, overall survival, and safety. Major organ deterioration-PFS (MOD-PFS) is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplantation, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring haemodialysis or renal transplantation), haematologic progression per consensus guidelines, or death (whichever came first).

The HR and CR rates were significantly higher in the daratumumab-VCd (dara-VCd) arm than in the VCd arm (HR 92% vs 77%, CR 53% vs 18%). There were also improved 6-month cardiac and renal response rates and MOD-PFS in the dara-VCd vs VCd arm (cardiac response 42% vs 22%, renal response 54% vs 27%, MOD-PFS hazard ratio 0.58 CI 0.3–0.93; $P=0.02$). At the last update presented at 2021 American Society of Clinical Oncology Annual Meeting, when the median follow-up for dara-VCd was 18.5 months and 5.3 months for VCd, the overall haematologic CR rate continued to be higher with dara-VCd than VCd (59% vs 19%; OR 5.9; 95% CI 3.7–9.4; $P<0.0001$). More patients achieved a $\geq$ VGPR with dara-VCd than VCd (79% vs 50%; OR 3.7; 95% CI 2.4–5.9; $P<0.0001$). Cardiac response rates were higher with dara-VCd than VCd at 6 months (42% vs 22%) and 12 months (57% vs 28%); renal response rates were 54% vs 27% at 6 months and 57% vs 27% at 12 months.

Of note, patients with severe cardiac impairment (NT-proBNP >8500 ng/L or New York Heart Association [NYHA] class 3B and 4) were excluded from the ANDROMEDA study. However, in a recent European Myeloma Network phase 2 study where NYHA class 3B patients with NT-proBNP >8500 ng/L were enrolled and received daratumumab monotherapy, the overall safety profile was

favourable with rapid and deep haematologic responses.⁴⁸ As such, daratumumab must be used cautiously as we await further emerging data.

In the ANDROMEDA study, treatment-related severe adverse events were comparable between the dara-VCd and VCd. However, the dara-VCd arm had higher rates of pneumonia (8% vs 4%) and overall incidence of grade 3 and 4 events (17 vs 10%). Though a minority of patients died in both arms, patients in the daratumumab arm had a numerically higher percentage of deaths attributed to adverse events. In contrast, disease progression accounted for more deaths in the VCd arm. The caveats in this study were the longer treatment duration in the dara-VCd arm compared to the VCd arm (18.5 months vs 5.3 months) and the exclusion of Mayo stage 3b patients. Despite the caveats, overall findings are promising, as the addition of daratumumab yielded significantly better outcomes, especially organ responses with manageable toxicities. Longer-term follow-up is needed to assess the impact on overall survival. Since a proportion of patients in the study in both arms went on to receive ASCT, comparing the outcomes in the transplanted group with and without added daratumumab will also inform future practice. Based on the ANDROMEDA results, the FDA approved the use of daratumumab in newly diagnosed AL amyloidosis, and recently, it received approval under the cancer drug listing in Singapore.

We suggest using VCd with or without daratumumab as possible options for induction treatment in newly diagnosed AL amyloidosis. However, the efficacy vs toxicity information, limitations of the ANDROMEDA trial, the cost involved, and patient preferences must be considered when deciding.

Immunomodulatory agents

Regimens using immunomodulatory agents (IMiDs) though effective, are generally avoided in AL amyloidosis, especially in frontline, as they are poorly tolerated and are also associated with a rise in cardiac biomarkers and worsening renal functions.⁴⁹ IMiDs such as thalidomide and lenalidomide have been studied in frontline therapy for AL amyloidosis and are effective, with one study demonstrating deep responses with upfront bortezomib, lenalidomide, dexamethasone (VRD) (HR 71%, VGPR/VR 44%). However, they are not the first-choice, upfront therapy due to the side effects, especially with increased rates of polyneuropathy with thalidomide,⁵⁰ fluid retention, rash, infections, high discontinuation rates and early mortality with lenalidomide, and risk of thromboembolic complications with both the agents.^{51,61}

There are phase 1 and 2 trials that demonstrate the efficacy of pomalidomide and dexamethasone, with HR rates reaching 48–50%, but with significant toxicities including grades 3 to 4 myelosuppression in 15–25% of patients, and grades 3 to 5 infection in 9–18% of patients.^{53,54}

IMiDs were generally reserved for use in relapsed refractory settings and even then, with abundant caution. However, patients with significant neuropathy who cannot have proteasome inhibitors can be considered for IMiD-based treatment options if other options, like daratumumab, are not applicable. Lenalidomide is administered at a reduced dose of 5–15 mg per day x 21 days and pomalidomide is administered at a starting dose of 2 mg, with patients closely monitored for worsening clinical status.

Duration of therapy

There are no randomised clinical trials to guide the optimal duration of induction treatment. However, as the median number of cycles achieved in clinical practice is 5, it has been suggested that induction therapy be continued for at least 6 cycles for patients with no coexisting MM or high-risk FISH abnormalities.³⁹ Patients with concomitant symptomatic myeloma or high-risk FISH abnormalities should be considered for 6–12 months of induction therapy and maintenance therapy after that.³⁹

Autologous stem cell transplant

Summary

- Consider high-dose chemotherapy with autologous stem cell transplant (ASCT) in all eligible patients.
- The timing of ASCT is to be decided on a case-by-case basis.
- Patient selection and assessment in a centre with experience performing ASCT in amyloidosis are paramount. In patients who are eligible but unlikely to tolerate full-dose melphalan, a risk-adapted approach may be considered at the discretion of the transplant physician.

The next consideration would be whether the patient is a candidate for high-dose chemotherapy followed by an ASCT. While there are no randomised control trials to support ASCT as a superior therapy, several observational studies that support the use of ASCT have reported high response

rates, durability of response and long-term survival. HR was achieved in 83–94% of patients, CR in 43–56%, and OR in 56–69%, with a median OS of 6.3–10.9 years.^{45,55–57} A retrospective analysis of the CIBMTR database identified 1536 patients with AL amyloidosis who had ASCT between 1995 and 2012. Over this period, there was an evident decline in early mortality and improvement in OS. Among the 800 patients transplanted from 2007 to 2012, the treatment-related mortality up to 100 days was 5%; the estimated OS rate at 5 years was 77%. Outcomes were better at centres that regularly performed more transplants for AL amyloidosis.³⁸

Optimal patient selection for ASCT is key to outcomes. Earlier studies had shown inferior outcomes with ASCT, mainly attributed to the higher early treatment-related mortality of approximately 24%.⁵⁸ However, with careful patient selection, medical advances in mobilisation, and peri-transplant supportive care, the transplant-related 100-day mortality has reached $\leq 5\%$.^{59,58} The CIBMTR pooled analysis and multiple single-centre studies have come to similar conclusions, with a decline in transplant-related mortality over the years and very good long-term OS in patients who can proceed with ASCT and achieve good responses.^{35,36,38,39,60} Patient selection is based on multiple factors, with the key determinants being patient-related clinical factors. One example from the European Hematology Association-International Society of Amyloidosis (EHA-ISA) working group is presented in Table 6 below.⁶¹ Whilst these are guidelines, familiarity, volume and experience of the transplant physician and centre (referral to a centre with specific expertise in transplanting AL amyloidosis), needs and wishes of the patient and an individual risk-benefit assessment are all important factors to consider when deciding to proceed with ASCT.

In patients deemed frailer with cardiac involvement, renal impairment or older age, dose-attenuated melphalan has been employed as a strategy. The use of a risk-adapted ASCT approach has been recommended in the EHA-ISA working group guidelines, to reduce toxicity and early transplant-related mortality⁶² (Table 7). This, however, needs to be weighed with the treatment efficacy as melphalan dose attenuation has been consistently shown to result in lower HR rates, inferior PFS and OS, and higher TRM rates and is an independent predictor for poor outcomes of ASCT.^{57,63} Consideration should also be given to infusing the stem cell product over 2 days to reduce the risk of infusion-related toxicity related

Table 6. European Hematology Association-International Society of Amyloidosis eligibility criteria for autologous stem cell transplant.

- Age >18 and physiological age <70 years
- At least 1 vital organ involvement
- Left ventricular ejection fraction $\geq 40\%$ and NYHA class <III
- Oxygen saturation $\geq 95\%$ on room air and DLCO >50%
- Supine systolic blood pressure ≥ 90 mmHg
- ECOG performance score ≤ 2
- Direct bilirubin <2 mg/dL
- NT-proBNP <5000 pg/mL
- troponin I <0.1 ng/mL, troponin T <0.06 ng/mL, hs-troponin T <75 ng/mL

Exclusion

- Medically refractory pleural effusions
- Stage 3b cardiac involvement
- Acquired factor X deficiency with active bleeding
- GI involvement with GI bleeding

DLCO: diffusing capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; GI: gastrointestinal; hs: high-sensitivity; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association

to volume and dimethyl sulfoxide content.⁶⁴

Bortezomib-based induction therapy is generally preferred in patients fit for ASCT prior to stem cell mobilisation and ASCT. While there is no consensus on induction therapy, in a Mayo Clinic study, induction therapy significantly improved post-ASCT response (CR from 18% without induction to 34% with induction) in patients with >10% plasmacytosis. However, there was no difference in HR or CR rates in those with $\leq 10\%$ plasmacytosis.⁶⁶

The optimal timing of ASCT, whether early or delayed, has yet to be discerned, as no clear difference in outcomes is seen between the 2 strategies. The role of ASCT in patients who have achieved CR after induction therapy remains unanswered; however, it has been found useful in patients with unsatisfactory responses to induction therapy. Experts have recommended stem cell collection, with the decision to proceed with ASCT

made on an individual patient basis. Patients who may benefit and therefore be considered for an early ASCT include those with high-risk FISH abnormalities, concomitant active myeloma, sub-optimal response to bortezomib-based induction therapy, and those with concerns for ineligibility if ASCT is deferred. Ultimately, the decision must be made based on individual patient assessment/circumstances. Our preference for frontline ASCT in all eligible patients is based on currently available non-randomised data suggesting that it can result in long-term remissions with manageable toxicity profiles. However, with the expanding armamentarium in the treatment of amyloidosis and increasing CR rates, the role of ASCT will have to be continually revisited (see discussion under the use of daratumumab).

Stem cell mobilisation in patients with AL amyloidosis is associated with a higher morbidity-mortality risk than MM due to risks of hypoxia, hypotension, capillary leak syndrome, cardiac or cardio-pulmonary decompensation and arrhythmias. Both chemotherapy and granulocyte colony stimulating factor (G-CSF)-based mobilisations are associated with higher grade 3–4 severe adverse events than MM. Some evidence supports the use of G-CSF and plerixafor as it is more efficacious, with less incidence of mobilisation failure and an overall reduction in G-CSF dose and associated complications like weight gain and fluid retention. This is particularly relevant in patients with impaired renal function and older patients with higher rates of mobilisation-related adverse events and failure. We recommend G-CSF with or without plerixafor for stem cell mobilisation for AL amyloidosis. If the patient has concurrent MM, chemotherapy mobilisation regimes are preferred. Overall, the higher cost of plerixafor and the potential benefit must be carefully weighed against the expected risk in an individual patient.^{61,67}

Table 7. Risk-adapted melphalan dosing for ASCT conditioning (adapted from EHA-ISA, Boston University⁶⁵).

	MEL200 ^a	MEL200 vs non-SCT regimes ^b	MEL140
Age (years)	≤ 60		>61
Cardiac stage	I	II	
eGFR (mL/min/m ²)	>50	30–50	≤ 30

eGFR: estimated glomerular filtration rate; MEL140: melphalan at the dose of 140 mg/m²; MEL200: melphalan at the dose of 200 mg/m²; SCT: stem cell transplantation

^a Requires all

^b Multidisciplinary discussion recommended

Maintenance therapy in AL amyloidosis

Summary

- Maintenance therapy after ASCT can be considered for patients with high-risk FISH abnormalities or myeloma phenotype (>10% plasma cells at diagnosis).
- Patients who did not achieve CR after ASCT could be considered for further continued therapy while balancing the risk of treatment-related toxicity.
- Decisions on treatment based on MRD results are not recommended at present and should be considered only in the context of a clinical trial.

There is a paucity of data on maintenance therapy after an autologous transplant; as such, it is currently based on expert opinion and may not be required for most patients who have an excellent response to ASCT. The goal of maintenance therapy is to maintain responses while balancing toxicity.

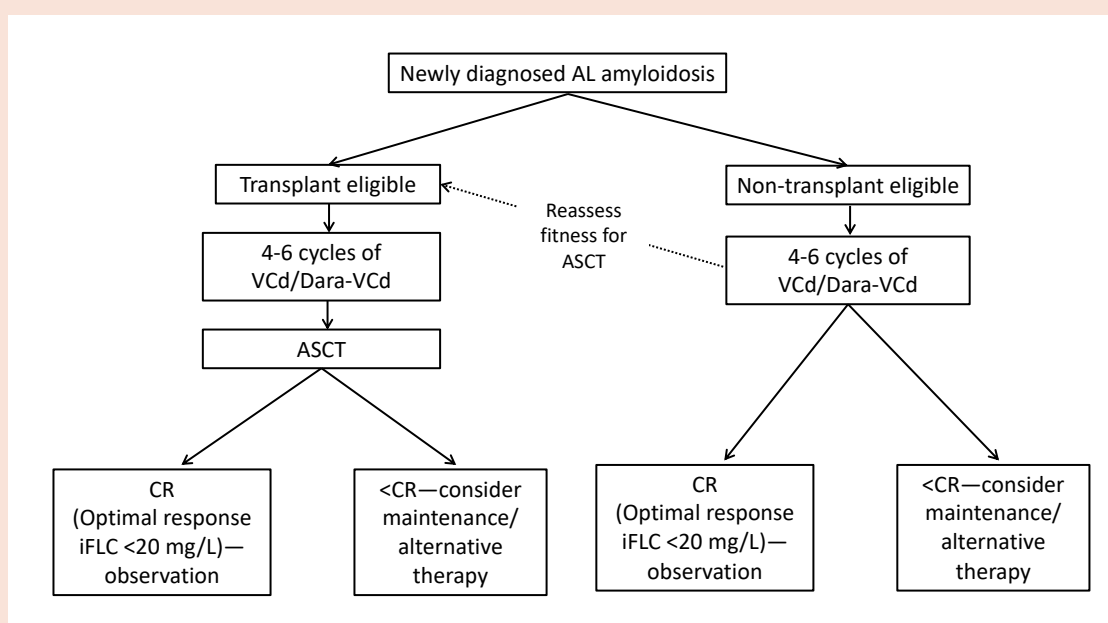
A single-centre prospective study⁹ with 19 patients who received 3 cycles of bortezomib/dexamethasone induction, or less if they have achieved a CR, followed by ASCT and 6 cycles

of bortezomib/dexamethasone consolidation, showed that each phase of treatment deepened the response, with overall achievement of high HR (95%) and MRD negativity (37%) rates, and durable 12 and 24 months PFS and OS (PFS 84% and 68%; OS 84% and 84%). Toxicities were manageable, with the main side effect being peripheral sensory neuropathy (53% G2-3 toxicity). This was likely due to intravenous administration of bortezomib, and the incidence would probably have been lower with subcutaneous bortezomib.

It was noted that none of the patients who achieved MRD negative CR progressed, with improved PFS, compared with patients without MRD negativity, 1 year after initiation of treatment. This suggests that strategies that deepen response may translate into improved long-term outcomes, thereby fulfilling the overall goal of therapy, specifically in patients with initially sub-optimal responses. However, these results need further larger-scale validation, and as such, decisions of treatment based on MRD results are not recommended in routine practice and should be considered only in the context of a clinical trial.

Similarly, in a retrospective study from the Mayo Clinic, 72 patients who underwent ASCT and received post-transplant therapy with either a proteasome inhibitor (PI), IMiD, or PI-IMiD

Fig. 2. Treatment algorithm for newly diagnosed AL amyloidosis.



ASCT: autologous stem cell transplant; CR: complete response; Dara: daratumumab; iFLC: involved free light chain; VCd: bortezomib, cyclophosphamide and dexamethasone

combination showed improvement in CR/VGPR from 35% to 58% with further therapy.⁶⁸

In the ANDROMEDA study, patients in the daratumumab arm received daratumumab maintenance for up to 24 months. Results from this study will further elucidate the role of maintenance therapy.⁴⁷

As this is currently a standard of care in patients with MM, Mayo mSMART guidelines proposed that patients with AL amyloid with concomitant MM phenotype or with high-risk FISH—del(17p), t(4;14), t(14;16), t(14p20, gain 1q)—should be considered for maintenance with preferably a PI.³⁹

Relapsed or refractory AL amyloidosis

Summary

- Daratumumab monotherapy with dexamethasone is the preferred salvage regime for patients not refractory to daratumumab.
- Bortezomib-dexamethasone is the preferred salvage regime for patients who are daratumumab-refractory, and bortezomib-sensitive. Ixazomib-dexamethasone is an alternative option.
- Lenalidomide-dexamethasone or pomalidomide-dexamethasone is the preferred salvage option for daratumumab and PI-refractory patients.

Starting second-line treatment for patients with AL amyloid is not a straightforward decision. Patients who do not achieve the optimal response of haematologic VGPR after first-line treatment should be considered for second-line therapy to further eliminate the plasma cell clone and achieve optimal OR. CIBMTR recommends that the assessment of HR requires 2 consecutive measurements made by the same method at any time before the institution of any new therapies.

No consensus exists on when treatment should be reinitiated at relapse. Most would agree that worsening organ function indicates the need for early initiation of therapy, as cardiac progression predicts shorter survival and renal progression predicts the early need for dialysis.⁶⁹ However, the decision to restart or change treatment due to rising iFLC before the development of organ progression, even if haematological progression is not met, is still a matter of debate (Fig. 3).

In a study by the Pavia group,⁷⁰ which looked at 259 non-transplant eligible patients, almost

two-thirds of patients who started second-line therapy had “high-risk dFLC progression”, defined as $\geq 50\%$ increase in dFLC from nadir dFLC achieved after frontline treatment, an absolute value of dFLC >20 mg/L; and a dFLC level that is $>20\%$ of the baseline value. “High-risk dFLC progression” precedes cardiac progression by a median of 6 months in 85% of cases, thereby identifying patients at high risk for relapse and in whom second-line treatment should be considered.

In a Mayo study⁶⁶ of 235 patients who relapsed after ASCT, it was found that the better the post-ASCT response, the longer the time to initiate the next therapy. Patients who did not achieve VGPR post-ASCT were more likely to have absolute values of dFLC that were higher at baseline and post-ASCT, and required second-line treatment. Patients with subtle haematological progression (who did not meet haematologic criteria for progression) from VGPR had a median of 2 years before organ progression, in contrast to patients with less than a VGPR post-ASCT who had 3–6 months to organ progression. Therefore, these findings confirm that even low concentrations of serum amyloid light chains are sufficient to result in the deterioration of organ function and inferior survival. It has been postulated that patients with at least a VGPR post-ASCT may tolerate a gradual rise in dFLC, especially if they did not have a dFLC of >50 mg/L at diagnosis. However, organ progression in some patients could occur as late as 8.3 years after haematologic progression.

Therefore, the individual patient’s performance status and potential treatment-related toxicity should be balanced with the desire to obtain the most profound responses when deciding to augment or restart therapy. Before starting salvage chemotherapy, re-evaluation of the patient’s disease with a repeat of serum and urine immunofixation electrophoresis, end organs including repeat cardiac scans, urine analysis and repeat bone marrow studies to look for residual disease by next-generation flow or other sensitive methods is recommended.

The data that are currently available for potential regimens at relapse is highlighted in the paragraphs that follow. However, the data are generally of low quality, i.e. retrospective single institutional experience or equivalent and do not provide much evidence regarding choosing one regimen over another. Hence the choice will be dictated by prior therapy, refractoriness to specific agents, expected toxicity of a regimen vs residual toxicities in a patient, drug accessibility as well as physician or patient preferences.

Daratumumab-based therapy is the preferred salvage regime for patients who are not refractory to daratumumab, given its high efficacy and tolerability. In the relapsed/refractory (RR) setting, haematologic responses with daratumumab and dexamethasone occur rapidly, within 1–3 months of therapy and are lasting with VGPR/CR rates in 60–80% and CR in 10–40% of patients.⁷¹ Currently available data have not shown added benefit in outcomes with the addition of other agents like bortezomib or IMiDs.

PI-based salvage regimen is preferred in patients who are refractory to daratumumab and bortezomib-sensitive. Bortezomib used in the salvage setting achieved good HR and CR rates (HR 70–80%, CR 15–40%).⁴⁶ Bortezomib can be combined with alkylator drugs like melphalan or cyclophosphamide in this setting. Ixazomib-dexamethasone is a plausible option, especially given the lower incidence of neuropathy than bortezomib. The Tourmaline-AL1⁷² phase 3 study comparing ixazomib-dexamethasone with physician's choice salvage regime (mainly comprising of melphalan-dexamethasone and lenalidomide-dexamethasone), however, did not meet its primary study endpoint of superior HR. However, patients treated with ixazomib-dexamethasone had better CR (26% vs 18%), organ response (36% vs 11%) and PFS (10m vs 5m) without OS advantage. Ixazomib may therefore be a potential option for PI-naïve patients with polyneuropathy.

Carfilzomib was used in a phase 1 study for relapsed AL amyloid but was associated with significant cardiac, renal and pulmonary toxicities; hence, it is not recommended for patients with cardiac or renal impairment and requires close monitoring and careful dose adjustments.⁷³

IMiDs are active in AL amyloidosis but are challenging to administer due to limitations by toxicities, as mentioned previously. Generally, lenalidomide and pomalidomide regimens are preferred over thalidomide regimens. They can be helpful in patients who are refractory to daratumumab and bortezomib or in patients with significant neuropathy, making bortezomib challenging. The doses used in AL amyloidosis are much lower than in MM—as lenalidomide doses greater than 15 mg/day was not tolerated. The most common adverse reactions include haematologic toxicities, rash, fatigue, infections and venous thromboembolism. In combination with an alkylator, lenalidomide yielded 40–60% HR, with 10% CR and infrequent ORs in most studies. A pomalidomide-dexamethasone study

of 87 patients with RR AL amyloid showed an HR in 68%, VGPR/CR in 29%.⁷⁴

Melphalan-based regimens (melphalan-dexamethasone or combined with bortezomib or lenalidomide) have also been used in relapsed settings and can produce responses.

Options for third-line salvage are limited—and these include any of the above regimens that patients are not refractory to, such as bendamustine, second ASCT in eligible patients and venetoclax in a subset of patients with t(11;14).

Venetoclax is effective in MM patients, especially those with t(11;14), as demonstrated in the phase 3 BELLINI study,⁷⁵ as approximately 50% of patients with AL amyloidosis harbour t(11;14), it is an appealing targeted treatment option.⁷⁶ The first retrospective study of 12 patients with RR AL amyloidosis in Mayo Clinic showed an ORR of 88% and CR of 44%, with manageable toxicities.⁷⁷ A second multicentre international, retrospective cohort study of 43 patients, reported 72% harbouring t(11;14). Patients with t(11;14), compared with patients who did not have the translocation had higher HR (81% vs 40%) and higher VGPR/CR rates (78% and 30%), with prolonged PFS (NR vs 6.7 months), with an increasing proportion of organ responses in patients with t(11;14). Grade 3 or high toxicity was 19%, with 7% being infection-related.⁷⁸ Overall findings demonstrate the efficacy of venetoclax in the RR setting for targeted treatment in patients with t(11;14) AL amyloidosis.

As T-cell engagers and chimeric antigen receptor-T cells are emerging as part of the armamentarium of myeloma treatment, further studies are necessary to elucidate their role in treating AL amyloidosis.

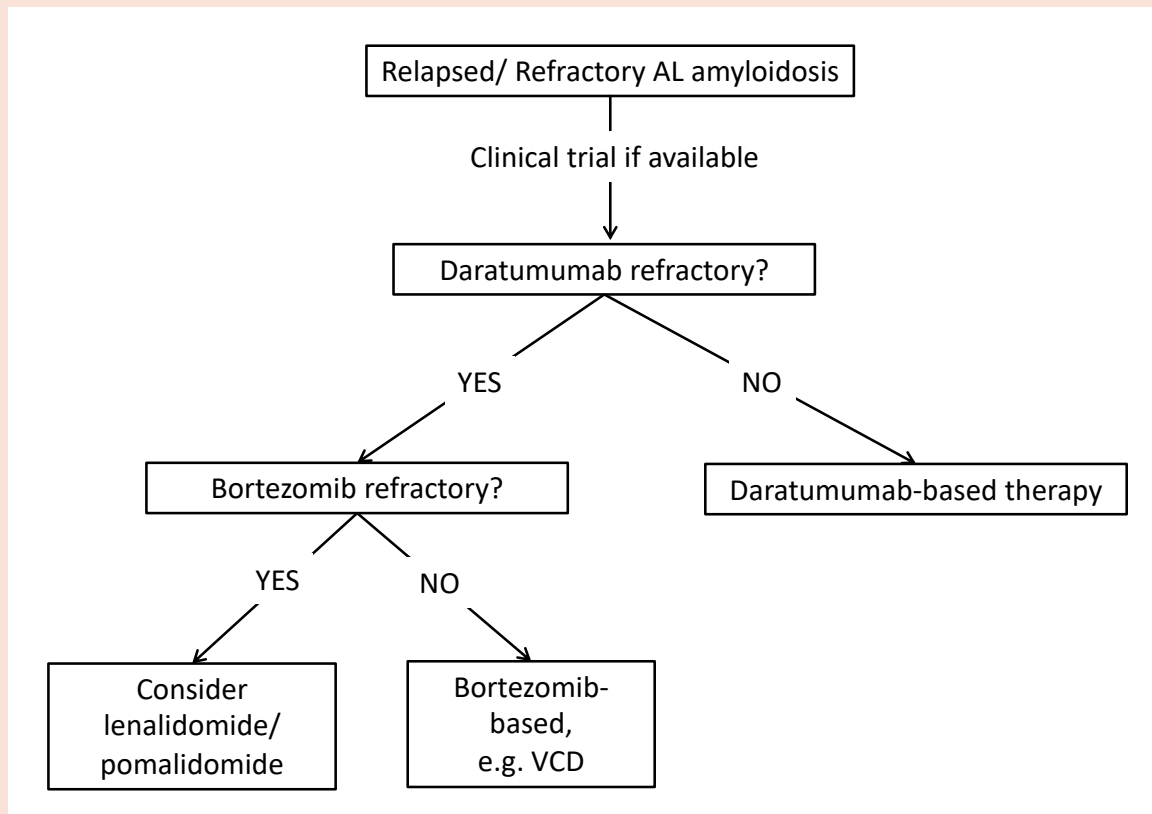
SUPPORTIVE THERAPY

As AL amyloidosis is often a multisystemic disease, it is imperative that a multidisciplinary approach be used for guiding management. This includes the involvement of cardiologists, nephrologists, neurologists, palliative care physicians and other specialists to help with symptom management. In addition, physical and occupational therapists and social workers also play a crucial role in providing appropriate support and advanced care planning.

Doxycycline

Pre-clinical studies have demonstrated that doxycycline has anti-fibril activity.⁷⁹ Additionally, 2 previous retrospective studies have also shown improved outcomes, and as such, is frequently recommended for patients with cardiac amyloidosis.

Fig. 3. Treatment algorithm for patients with relapsed refractory AL amyloidosis.



VCD: bortezomib, cyclophosphamide and dexamethasone

The first is a case-control study of patients with AL amyloidosis, including those with Mayo stage 3a disease treated with standard chemotherapy. The HR rate was significantly higher in the doxycycline group as compared with the control group (93% vs 59%), with higher CR rates (56% vs 35%), higher cardiac response rates (60% vs 18%) and improved 24-month survival (82% vs 53%).⁸⁰

The second study from Mayo Clinic looked at patients who received doxycycline post-ASCT as part of the antibiotic prophylaxis given penicillin allergy.⁸¹ In the initial 2012 analysis, a survival advantage was demonstrated in patients who achieved HR. However, a recent update after 12.7 years of follow-up of the same cohort showed a non-statistically significant trend towards improved survival with doxycycline among patients with VGPR or better or with OR.⁸² In another recent multicentre randomised control trial in China where patients were randomised to doxycycline with VCD for 9 cycles vs VCD alone, the addition of doxycycline failed to show improved PFS or cardiac PFS.⁸³ Therefore, with evolving evidence, the role of doxycycline will need to be revisited.

Management of cardiac failure or complications

Summary

- A combination of loop and mineralocorticoid receptor antagonists should be used to treat fluid overload.
- Beta-blockers and ACEi/ARBs should be avoided or used cautiously due to risks of profound hypotension.
- Digoxin may be used cautiously for rate control of AF with frequent monitoring of digoxin levels/toxicity. Amiodarone and ablation are plausible options. Further discussion with a cardiologist is suggested.

The treatment of heart failure resulting from cardiac AL amyloidosis is a therapeutic challenge due to the complex nature of cardiac dysfunction, and concurrent renal and autonomic comorbidities. Diuretics are the primary treatment for managing fluid overload due to congestive heart failure, nephrotic syndrome or therapy. Combining

loop diuretics and mineralocorticoid receptor antagonists like spironolactone often yields the best results. However, doses are limited by the risk of symptomatic hypotension and worsening renal function. Therefore, careful titration with close monitoring of tolerance, renal function, and electrolytes should be performed upon initiation of therapy. Careful employment of oral vasopressors like midodrine could help minimise symptomatic hypotension and maintain blood pressure. Lifestyle measures such as fluid and salt restriction are also critical. Albumin infusions may be helpful if there is concomitant severe nephrotic syndrome.

In patients with cardiac amyloidosis, the underlying pathology is often severe diastolic dysfunction with preserved ejection fraction but reduced stroke volume due to restrictive filling⁸⁴. Therefore, they depend on higher heart rates to maintain cardiac output. Standard medications often used to treat patients with heart failure with reduced ejection fraction, specifically beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), often worsen the patient's clinical condition. Beta blockade may result in profound hypotension, reduced cardiac output, or worsened renal functions in patients with cardiac AL amyloidosis. A multidisciplinary approach involving collaboration with cardiologists and renal physicians is valuable in managing these patients.

Patients with atrial fibrillation (AF) often cannot tolerate beta-blockade or calcium channel blockers traditionally used for rate control. Digoxin may be safely used in low doses, but caution should be taken to monitor electrolytes and kidney function closely.⁸⁵ Digoxin toxicity has been reported in AL amyloidosis, even at therapeutic doses, due to the drug binding and affinity to amyloid fibrils.⁸⁵ Amiodarone is the preferred alternative, albeit with insufficient evidence. Ablation of the atrioventricular node with permanent pacing may be advantageous for a subset of patients.³⁹ In some cases, no rate control agent is required if there is concomitant conduction system disease.

Sudden cardiac death in patients with amyloidosis has been reported in 15–23% and is commonly due to pulseless electrical activity often preceded by bradycardia.⁸⁶ The role of implantable cardioverter-defibrillators is controversial, and appropriateness needs to be decided by the cardiologists closely involved in the management of such patients.

Studies have shown a high prevalence of intracardiac thrombus in cardiac amyloidosis in up to 35% of patients with AL amyloidosis.⁸⁷ Most thrombi are found in the right or left atrial appendages (LAA). AF and echocardiography

variables of left ventricular diastolic dysfunction and low LAA emptying are independent variables associated with intracardiac thrombus. In the setting of AF, anticoagulation should be considered independent of the CHA₂DS₂-VASc score to reduce thromboembolic risk. This, however, has to be weighed against the increased risk of bleeding, especially in patients with gastrointestinal (GI) involvement and coagulopathy.⁸⁷

Management of renal failure or complications

The median time from diagnosis of patients with AL amyloidosis and nephrotic syndrome to dialysis is 14 months, with one-third requiring dialysis.⁸⁹ The mainstay of treatment of oedema is with diuretics. ACEI may reduce proteinuria in patients with proteinuria, but careful monitoring of electrolytes—given the risk of hyperkalemia—is necessary.⁹⁰ Dialysis in these patients can be challenging as many may have concomitant cardiac amyloid or orthostatic hypotension with recurrent intradialytic hypotensive episodes. Construction of an arteriovenous fistula may also have increased bleeding risk, especially in patients with coagulopathy or vascular and cutaneous amyloid.⁹¹

Management of GI complications

Some common symptoms of GI involvement in AL amyloidosis include alternating diarrhoea and constipation, weight loss, heartburn and nausea, and up to 50% may present with GI bleeding. In patients with dysmotility symptoms, nutritional supplementation and dietary modification—including frequent small-volume liquid or homogenised foods with low soluble fibre and fat, and prokinetic agents such as metoclopramide, erythromycin or domperidone—are advised. For patients with diarrhoea, anti-diarrhoeal such as loperamide can be initiated.

Organ transplant

Summary

- In exceptional cases, organ transplants (i.e. heart and kidney) can be considered.

Solid-organ transplantation is controversial in organ failure in AL amyloidosis, given concerns that the AL amyloid might recur in the transplanted organ. This is corroborated by multiple case series demonstrating recurrent AL amyloid in the transplanted heart and kidney.^{86–92} Outcomes of cardiac transplant for AL amyloid are poorer than non-amyloid patients, with a 5-year survival of 43% vs 85%, respectively, with most deaths occurring from progressive amyloidosis.⁹³ However,

later studies have shown that with improved chemotherapy regimes and novel agents, cardiac transplant outcomes in AL amyloidosis improved.⁹⁴

Mechanical circulatory support (MCS) is a feasible option in patients with acceptable outcomes as a bridge to transplantation.⁹⁵ With highly effective clone-directed therapies like daratumumab, salvaging patients presenting with more severe cardiac failure by temporarily employing left ventricular assist devices allowing for adequate organ function recovery has become a reality even in our local setting.^{96,97} However, given the limited resources and morbidity related to MCS, it remains the exception rather than the norm.

In a large series of AL amyloid patients who have undergone kidney transplantation, potential good outcomes can be achieved with patients who have achieved CR or VGPR at the time of kidney transplantation.⁹⁸ Recent consensus guidance by the American Society of Transplantation suggested some criteria for proceeding with renal transplant⁹⁹ (Table 8).

Table 8. American Society of Transplantation organ transplant consensus for AL amyloidosis.

Criteria for organ transplantation in amyloidosis	Therapeutic response with dFLC of <40 mg/L
	Only 1 organ involved with amyloidosis
	Does not fulfil criteria for symptomatic myeloma
	Must be a candidate for stem cell transplantation following organ transplantation

dFLC: difference between involved and uninvolved free light chain

Neuropathy or autonomic dysfunction

Summary

- Neuralgesics can be used effectively in patients with neuropathy.
- Non-pharmacological methods (compression stocking, abdominal binders, exercise) and pharmacological methods (midodrine, pyridostigmine) can treat neurogenic orthostatic hypotension.

Peripheral neuropathy is a common presentation in 9.6–35% of patients. The pattern of involvement is symmetrical, length-dependent, lowed-limb neuropathy that is slowly progressing and painful.¹⁰⁰ Symptomatic treatment with neuralgesic agents

including gabapentin, pregabalin, amitriptyline, nortriptyline or duloxetine should be considered for relief of discomfort. In patients with carpal tunnel syndrome, surgical carpal tunnel release or braces may benefit.³⁹

Treatment of patients with orthostatic hypotension and secondary autonomic dysfunction may be challenging in patients with severe nephrotic syndrome or cardiomyopathy. Non-pharmacological therapy includes compression garments like compression stockings and abdominal binders, and regular exercise may benefit. Pharmacological treatment, including alpha-1 adrenergic receptor agonist midodrine or anticholinergic pyridostigmine may improve neurogenic orthostatic hypotension.¹⁰¹ Fludrocortisone 0.1 mg twice a day or three times daily must be used cautiously as it may aggravate congestive heart failure. In patients with symptoms associated with gastroparesis, metoclopramide may be considered.

DRUG TOXICITY AND DOSE ADJUSTMENTS

Recommendations

- Administer bortezomib once weekly subcutaneously.
- Close monitoring for toxic effects, including cardiac toxicity, hypotension, neuropathy.
- An initial lower dose of bortezomib and dexamethasone can be considered before dose escalation, if tolerated, to avoid excess toxicity in patients with advanced heart disease (Mayo stage 3b).

Bortezomib should be administered subcutaneously once weekly at an initial dose of 1.3 mg/m². A once-weekly bortezomib dosing was associated with a better toxicity profile than twice-weekly bortezomib, including fewer cardiac events, orthostatic hypotension, and dose modifications.⁴⁶ Risk-adapted dosing strategies may help abrogate the risk of early mortality. One such strategy—using bortezomib 1.3 mg/m² on days 1, 8 and 15 with dexamethasone 20–40 mg on the same days, compared to a standard dose of 1.3 mg/m² plus dexamethasone 40 mg on days 1, 4, 8 and 11 every 21 days for up to 8 cycles—significantly lowered 3-month death rates (4.5% in the dose-adjusted group vs 36%) in patients with Eastern Cooperative Oncology Group performance status ≥2, or cardiac dysfunction (Mayo stage 2 with proBNP > 1285 ng/L or Mayo stage 3), or age >70 years, or pre-existing peripheral neuropathy due to AL amyloidosis, or symptomatic orthostatic hypotension with systolic blood pressure at erect

Table 9. Dose adjustments suggested for patients with renal impairment.

Creatinine clearance	Dose adjustment for CrCl	Timing of administration if on dialysis
Bortezomib - Any CrCl	No	After dialysis
Cyclophosphamide - CrCl <10 or dialysis	75% dose	After dialysis
Oral melphalan (IMWG) - CrCl 15–59 - CrCl <15 or dialysis	- 75% dose - 50% dose	Before or after dialysis
Dexamethasone - Any CrCl	No	Before or after dialysis
Aciclovir - CrCl 10–25 - CrCl <10 or dialysis	- No adjustment or reduce to 200 mg q12h - 200 mg q12h	After dialysis
Co-trimoxazole - CrCl 15–30 - CrCl <15 or dialysis	- 50% of usual dose - Approx. 25–50% of usual dose. Use with caution.	After dialysis
Daratumumab	No	Before or after dialysis

ASCT: autologous stem cell transplant; CrCl: creatinine clearance; IMWG: International Myeloma Working Group

position <100 mmHg.¹⁰² HR and CR rates were comparable in patients who received risk-adjusted vs standard doses of bortezomib/dexamethasone.

Dose adjustments in patients with renal impairment

Patients with renal impairment or on long-term dialysis will require adjustment of therapy (Table 9).

CONCLUSION

The current guidelines aim to provide a comprehensive review of the diagnosis and management of patients with AL amyloidosis in Singapore. As AL amyloid is a rare disease with a paucity of large-scale clinical trial data to inform therapy, referral to a centre with expertise in treating AL amyloidosis would be recommended from the point of clinical suspicion or diagnosis.

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