

Improving management of AL amyloidosis

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In this issue of the *Annals*, Tan et al. on behalf of Singapore Myeloma Study Group presented the consensus guidelines on light chain (AL) amyloidosis.¹ This is an encouraging effort as AL amyloidosis is a rare disease, with diagnostic and therapeutic challenges. A comprehensive review examining its pathophysiology, diagnostic approach, and management by a multidisciplinary team will set the minimum bar for treatment outcomes of patients, taking into account advances in clinical management.

Amyloidosis is a disease caused by deposition of abnormal protein fibrils affecting multiple organs, such as heart, kidney, gut, etc. This causes a myriad of clinical presentation from proteinuria to life threatening/refractory heart failure. Amyloidosis remains challenging to diagnose and treat,² and a negative biopsy result does not exclude the diagnosis. Contributing to this is the presence of culprit plasma cells that only comprise a small fraction (a few percentages) of bone marrow population compared to myeloma where there will be a significantly increased abnormal plasma cells. The development of flow cytometry helps to identify confidently the abnormal plasma clone even at low percentage. Recent advances, such as serum free light chain analysis and mass spectrometry also help to address these limitations to confirm the diagnosis promptly and accurately. This was discussed in detail in the manuscript and can help in guiding the diagnostic process as well as in staging, which help predict the outcome of AL amyloid patient.

Meanwhile, raising disease awareness among general physicians and enabling early diagnosis are of paramount importance. Tan et al. provides guidance via an algorithm on how to work-up individuals with high suspicion of AL amyloidosis—particularly providing consensus on organ involvement, which is beneficial for all treating physicians. There are also suggestions for alternative approaches in cases where mass spectrometry analysis is not available or affordable.

In the context of various induction treatments, bortezomib-based regimens, with or without daratumumab, are recommended. Additionally, it highlights the importance of carefully selecting the right patients for autologous transplantation.

However, the prognostic value of genomic markers in patients with AL amyloidosis is still under validation. For instance, consider t(11;14) in patients with AL amyloidosis, which is considered a standard prognostic marker in multiple myeloma (MM) but is associated with relatively poor outcomes in AL amyloidosis when treated with (VCD). A recent retrospective analysis further supports these findings.³ Consequently, it is advisable to routinely screen for t(11;14) in patients with AL amyloidosis, not only due to its high incidence (at approximately 50%) but also because it influences the choice of treatment regimen. Nonetheless, an unmet need persists for treatment recommendations specific to this patient subgroup, as the VCD regimen is generally recommended. Venetoclax may offer an alternative, having shown effectiveness in MM patients, particularly those with t(11;14), as demonstrated in the phase III BELLINI study. However, this study did indicate higher mortality in non-t(11;14) patients. Furthermore, no significant difference was observed in progression-free survival (PFS) in the updated results from the phase III CANOVA study comparing venetoclax/dexamethasone and pomalidomide/dexamethasone in relapsed or refractory MM patients.⁴ Therefore, further research is essential to develop more precise guidelines, moving from the current autologous transplantation or not decision towards the consideration of genetic markers, such as t(11;14), in treatment selection for AL amyloidosis patients.

The outcome for AL amyloidosis has improved significantly from diagnostic tools, treatment as well as multidisciplinary supportive care for patients. There are 3 main aspects in the management of amyloidosis—to eradicate the abnormal plasma clone rapidly; to support the affected organ until the amyloid deposit dissolves from the affected organs and to reduce the amyloid deposit in organs involved. While there are encouraging progress made in the first 2 aspects, there has yet to be significant progress in the latter.

The article by Tan et al. reviewed the treatment armamentarium for AL amyloid. Treatment of AL amyloid made first significant progress when bortezomib was used to control the abnormal

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plasma clone and to eliminate “the source” of the amyloid fibril. Following this success, further improvement was made when monoclonal antibody against plasma cells (CD38 antibody) was added to target this clone more specifically and rapidly with lesser side effects. Monoclonal antibody may even replace the role of autologous stem cells transplant in AL amyloid in future.

Remarkable medical progress was achieved in many fields to support AL amyloid patient, such as in cardiology, nephrologist, infective disease etc. These supports are important as the amyloid fibril deposit dissolve slowly from affected organs and multidisciplinary intensive support is needed. In fact, multidisciplinary approach is the key to ensure good outcome for amyloid patient.

Finally, one the remaining key challenge in amyloidosis is on how to dissolve or extract out the deposited amyloid fibril from organs rapidly to improve organ function. There are few potential medications in clinical trial that have been shown to be able to reduce the organ impairment rapidly.⁵ However, these are not available in clinical practice and we hope this will make the next wave in the management of amyloid patients soon. Interestingly, doxycycline antibiotics was shown to help in dissolving amyloid fibril in mouse model as well as in trial involving a small number of participants. However, in larger trial this was not shown to have additional benefit. It is fair to say doxycycline was also not shown to increase side effects on treatment. In view of the limited agent available, it is fair to consider this as supporting medication if the patient can tolerate doxycycline without significant side effects.

AL amyloidosis is a complex disease requiring high clinical suspicion with multidisciplinary collaboration; a proper diagnostic approach; early

access to supportive care for organ failure and new targeted therapy to improve outcome. The guidelines by the Singapore Myeloma Study Group provide evidence-based recommendations for use with sound clinical judgement by haematologists and other relevant specialists, in diagnosing and managing AL amyloidosis in Singapore. The group’s proposed algorithm for when clinical suspicion of amyloidosis is raised, provides guidance for careful work-up of patients to ultimately lead to an early diagnosis and overall survival of patients. We have improved significantly in the management of AL amyloidosis over the past decade and are at the brink of another breakthrough for the eureka moment in treating this challenging disease.

Keywords: AL amyloid, cancer, evidence-based, guideline, haematology

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