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How I manage systemic light chain amyloidosis

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Abstract

Light chain amyloidosis (AL) is a protein deposition disorder with a heterogeneous pattern of organ involvement and dysfunction that varies by affected patient. Often diagnosed late after the onset of symptoms, appropriate and correct diagnosis, and prompt initial management, typically with anti-plasma cell therapy targeting the underlying cell producing the aberrant light chain protein, can lead to significant improvement in patient symptoms, organ function and lifespan. With recent publication of phase III studies focused on AL, and a changing regulatory landscape providing greater availability of novel therapies, the management of AL is in some ways more complex with greater options to consider. In this clinical review, a discussion of the diagnosis, staging, and goals of therapy transitions to a focus on contemporary management questions to outline our clinical approach to multi-disciplinary management and long term follow up for patients with suspected or confirmed AL.

Introduction

Amyloidosis caused by deposition of misfolded light chain fibrils, or AL amyloidosis, is often found with an underlying low-grade plasma cell population in the bone marrow, though also occurs in a portion of patients with multiple myeloma, and less commonly other indolent hematolymphoid cancers. The incidence and prevalence of AL have been approximated from population studies in the US and Europe to an estimated 3-14 cases per million-person years, with an estimated 12,000 people currently living in the US.⁽¹⁻³⁾ In the systemic form of the disease, common organs affected include the heart, kidneys, liver, peripheral and autonomic nervous system, and gastrointestinal tract. This involvement leads to clinical symptoms associated with nephrotic syndrome, cardiomyopathy, hepatomegaly, neuropathy, carpal tunnel syndrome and easy bruising with frequent periorbital purpura.⁽⁴⁾ While a delay in diagnosis is common, due to symptoms being vague or overlapping with other common disorders, data suggests this may be exacerbated by racial disparities in healthcare outcomes. One study found black patients in the US having more suggestive findings such as the presence of MGUS, and diagnoses of organ dysfunction such as cardiomyopathy and chronic kidney disease, prior to the unifying diagnosis of AL being reached compared to white patients.⁽⁵⁾

Obtaining the correct diagnosis and accurately assessing the evidence of systemic involvement is key to ensuring proper treatment for patients with suspected AL. Given that we now have approved therapies for other amyloidosis subtypes including wild type (ATTRwt) and hereditary ATTRv) transthyretin amyloidosis which often involve the heart as well as peripheral and autonomic nervous systems respectively, proper subtyping and understanding of diagnostic testing is imperative. Technetium Tc 99m Pyrophosphate scanning, has been shown to have up to a 94% sensitivity and 89% specificity in detecting cardiac amyloid due to ATTR disease (typically is negative or not strongly positive in AL cardiomyopathy), though testing for monoclonal paraproteins is still recommended, and if present we pursue endomyocardial biopsy to differentiate the etiology.⁽⁶⁾ Laser microdissection and mass spectrometry-based proteomic analysis remains the optimal gold standard for amyloid subtyping.⁽⁷⁾ However, we try to emphasize that diagnostic information can be gleaned from immunofluorescence

studies as well as electron microscopy, though weak staining or lack of predominance for kappa or lambda light chains with immunostains can often be seen and should not exclude the possibility of AL disease.⁽⁸⁻¹⁰⁾ Differentiating systemic AL from focal amyloid deposition is also crucial in identifying patients who will benefit from plasma cell directed therapy. We note two specific populations of interest here, the first with evidence of AL amyloidosis identified in the bone marrow or fat aspirate without evidence of other organ or extensive soft tissue involvement. In a study of 117 patients with amyloid deposits fitting this criteria, 52 patients did not require systemic therapy for another plasma cell neoplasm indication and among these patients there was no progression over a median of 2.5 years to systemic AL with organ involvement requiring therapy.⁽¹¹⁾ Thus, while the subcutaneous fat and bone marrow are sites of interest for the diagnosis and typing of amyloid deposits, in and of themselves should not be seen as an indication for therapy for systemic AL. The other population of interest is patients with localized or focal AL deposits, typically occurring in the aero-respiratory tract, bladder, breast, or other areas without evidence of typical organ involvement. These focal AL patients have an observed low rate of around 1% for progression to systemic AL and have been found to have excellent 10-year OS rates of 92% with most deaths attributable to other causes.^(12, 13)

Prognosis in systemic AL is driven by the degree and severity of cardiac involvement, though even patients with advanced cardiac AL can significantly benefit from promptly administered plasma cell directed therapy. However, beyond survival, appropriate therapy can improve the chronic symptoms relating to the morbidity of amyloid organ involvement and decrease in quality of life these patients incur. Several staging systems have been proposed for cardiac AL prognosis, though we find the European modification of the original Mayo staging system to be most useful in clinical practice.⁽¹⁴⁾ In the original analysis to develop this staging system it should be noted that only a minority of patients (<10%) received frontline bortezomib based therapy, and this was prior to the development and availability of anti-CD38 monoclonal antibodies including daratumumab. This modification looked at further stratifying patients with stage III cardiac AL based on the original 2004 Mayo Clinic model for patients with elevated NT-proBNP and troponin T by identifying patients with stage IIIB disease as those with NT-proBNP >8500 ng/L.⁽¹⁵⁾ Patients with IIIB cardiac AL with baseline systolic blood pressure <100 mm Hg were found in this retrospective study to have a median OS of only 3 months. Many of these early deaths were in patients who were not able to be successfully treated and did not obtain hematologic response, emphasizing the importance of early diagnosis and prompt treatment. A rapid and deep hematologic response as early as 1 month into treatment has been shown to carry a survival benefit with a landmark analysis carried out by a European consortium of AL patients treated primarily with bortezomib based therapy.⁽¹⁶⁾ A comparison of prognostic models, using the original 2004 Mayo Staging system, 2012 revised Mayo Stage which introduced dFCL as a covariate with high dFLC being an adverse prognostic factor, and the European modification of the 2004 Mayo system showed general agreement, with the European model showing improved prediction of early 1-year mortality.⁽¹⁷⁾ We find it clinically useful to identify patients who have stage IIIB cardiac AL as these patients have been excluded from some key prospective interventional studies, and are now being evaluated as a separate population from the standpoint of clinical trial eligibility for targeted interventions given the poor prognosis and high risk of early death in this population.⁽¹⁸⁾ In our practice we often use cardiac MRI at baseline for patients with suspected cardiac dysfunction, as T1 and T2 mapping combined with

determinants of extracellular volume (ECV) are powerful predictors of outcomes, and can be followed serially to provide additional information on cardiac response beyond serum NT-proBNP and echocardiographic findings.⁽¹⁹⁾

The aim of therapy in AL is to improve and stabilize organ function, and improve patient quality of life and survival. Prompt initiation of plasma cell directed therapy which, when indicated can drive deep hematologic responses has been shown to correlate with biomarker-based organ responses and overall patient survival.⁽²⁰⁾ Historically, response criteria were validated in patients with dFLC levels >50 mg/L, denoted as measurable hematologic disease which 90% of newly diagnosed systemic AL patients meet, though a minority of patients with low dFLC have separate hematologic response criteria defined as achieving dFLC <10 mg/L.⁽²¹⁾ Recent analysis of achieving a dFLC of <10 mg/L was validated in a broader cohort of systemic AL patients including those with baseline measurable disease, and has been termed stringent dFLC response, with superior outcomes among this population as compared with historical VGPR based outcomes.⁽²²⁾ In practice we focus on patients obtaining a VGPR (dFLC < 40 mg/L) hematologic response or greater as the upfront goal of plasma cell directed therapy. Organ response assessment has been historically based on serum and urine biomarkers. A cardiac response requiring a 30% or greater reduction in NT-proBNP level with absolute reduction of >300 ng/L, and a renal response requiring a 50% reduction of at least 0.5 g/day of proteinuria on a 24-hour urine collection without increase in creatinine clearance of 25% above baseline.⁽²³⁾ Beyond these binary cutoffs, graded organ response criteria have been proposed that show correlation with improved survival with deeper improvement in organ function.⁽²⁴⁾ While prognostic, the ramifications on treatment are not fully understood and the current aim of plasma cell directed therapies continues to be a deep hematologic response, though we recognize a population of need remains who have persistent organ dysfunction and related symptoms despite achieving targeted hematologic response. Ongoing areas of interest include the incorporation of bone marrow and serum based minimal residual disease (MRD) techniques, and improving understanding of how obtaining MRD negativity may yield additional marginal benefit in patient outcomes.^(25, 26)

Management Dilemmas

What is the optimal frontline therapy for newly diagnosed systemic AL?

For patients with newly diagnosed systemic AL, prompt treatment with the aim of deep hematologic response remains the primary goal with systemic therapy. For patients with advanced cardiac involvement, close management with a cardiologist experienced in the management of AL cardiomyopathy is important for volume status management, hypotension, and management of dysrhythmia. Based on retrospective studies and clinical experience, the combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) had evolved to become a standard of care for newly diagnosed AL amyloidosis.^(27, 28) Since the broader availability of daratumumab for multiple myeloma in the US in late 2015, retrospective and prospective data emerged that showed acceptable safety and improved depth of hematologic response compared to historical expectations with the use of daratumumab in previously treated systemic AL.⁽²⁹⁻³¹⁾ Additionally, clinically meaningful organ

responses in patients with these daratumumab induced hematologic responses, in the setting of previously treated disease were seen.⁽³²⁾ Given these encouraging findings, the *ANDROMEDA* study evaluated subcutaneous daratumumab in combination with CyBorD as compared with CyBorD alone in patients with newly diagnosed systemic AL.^(33, 34) Of note, patients with stage IIIB disease (baseline NT-proBNP >8500 ng/L), or with systolic blood pressure measuring less than 90 mm Hg, were not included in the *ANDROMEDA* study. Over sixty percent (63.3%) of patients treated with daratumumab plus CyBorD achieved a dFLC <10 mg/L, compared with just 29.5% of patients treated with CyBorD alone. Rates of hematologic VGPR were 78.5% in the daratumumab arm compared with just under half of the CyBorD alone treated patients. These hematologic responses translated into improvements in cardiac and renal responses at six months in favor of the daratumumab containing arm, with 41% vs 22% of patients obtaining cardiac responses and 53% vs 24% obtaining renal responses. Still, the risk of early death was similar in both arms, almost exclusively in patients with advanced cardiac involvement with 13 patients in each arm dying within 30 days and overall 27 versus 29 patients dying at the report of the study primary outcome. There is yet no difference in overall survival between the groups. Still, our view is that the incorporation of daratumumab into frontline bortezomib containing regimens provides a significant advantage, as for the first time we are able to obtain meaningful deep hematologic responses in the majority of systemic AL patients.

The question of the need for cyclophosphamide and optimal dose of dexamethasone in the frontline treatment of systemic AL is an active one. Some data have suggested that cyclophosphamide and higher doses of dexamethasone do not add benefit to bortezomib containing therapy.^(35, 36) We are currently also examining the regimen of daratumumab in combination with ixazomib and dexamethasone as both frontline and subsequent therapy for systemic AL (NCT03283917). At the current time, and given its FDA approval in the United States, we include subcutaneous daratumumab in combination with CyBorD for patients with systemic AL in need of frontline therapy. While other written guidelines sometimes suggest a pathway for autologous stem cell transplantation in select patients as initial therapy based on bone marrow plasma cell percentage, we practically find that this would create a delay in therapy, and consider autologous stem cell transplantation with high dose melphalan following initial assessment of response to frontline daratumumab plus CyBorD. For patients with stage IIIB disease who were not included in the *ANDROMEDA* study, typically due to NT-proBNP >8500, we aim to enroll on trials targeting these patients specifically or when not an option consider close observation with initiation of daratumumab plus CyBorD therapy in the hospital, often with a dose reduction of bortezomib for the first cycle.

What is the current role of autologous stem cell transplantation for these patients?

High dose chemotherapy and autologous stem cell transplantation (HDT-AuSCT) has been in use since the early 1990s and is a proven treatment modality in AL with hematologic and organ responses as well as long term survival data to support its use.⁽³⁷⁻³⁹⁾ Some studies have reported increased rates of treatment-related mortality (TRM) as high as 24%, typically in patients with advanced cardiac involvement, though in our experience with careful patient selection these mortality rates are lower at 3-5%, though still increased compared to patients with multiple myeloma.⁽⁴⁰⁾ The track record of proven decades long

favorable outcomes for patients with AL, who often are observed without maintenance therapy after HDT-AuSCT, is one advantage that we cannot yet claim to know with daratumumab based therapies in the upfront setting.⁽³⁹⁾ In the *ANDROMEDA* study, patients were not planned for autologous stem cell transplant, and those randomized to the daratumumab arm continued with maintenance monthly daratumumab through month 24. In the CyBorD alone arm, only 10.6% of patients received subsequent stem cell transplantation whereas this was only 6.3% of patients in the daratumumab containing arm.

HDT-AuSCT following induction chemotherapy has been shown to be a proven treatment strategy following bortezomib based therapy.⁽⁴¹⁻⁴³⁾ In a planned response adapted study using bortezomib based induction therapy followed by HDT-AuSCT in patients with insufficient hematologic response, of 139 patients initially treated with CyBorD, 55 patients (40%) ended up undergoing AuSCT a median of 5 months following initiation of CyBorD. In this subgroup of patients with inadequate response to CyBorD induction, 65% obtained a VGPR or deeper hematologic response following AuSCT. In practice, with the increased use of daratumumab-CyBorD therapy in the frontline setting, we individualize the evaluation and consideration of HDT-AuSCT following initial response assessment. Typically after the first two cycles of therapy, patients obtaining deep hematologic complete response or stringent dFLC response are considered to defer HDT-AuSCT which could then be used as a salvage therapy option if needed in the future.⁽⁴⁴⁾ However, our practice still favors HDT-AuSCT as consolidation after induction in most patients, with an added benefit of upfront daratumumab-CyBorD therapy being that the clinical improvement seen with deep early hematologic response and organ improvement, which may allow previously transplant ineligible patients to be eligible for AuSCT and may ameliorate the risk of TRM in patients as well, via improvement in organ function compared to baseline. Still, we acknowledge that future studies are needed to define which subgroups of patients see the most benefit from HDT-AuSCT, with a particular focus on those who achieve deep hematologic responses with systemic induction therapy. The use of MRD techniques in this setting is being actively explored as well.

What is insufficient response? What does relapse look like? And when is a change in treatment warranted?

The goal of initial therapy in AL is to obtain a deep hematologic response. For patients who fail to obtain a hematologic VGPR with upfront therapy, we move quickly to modify therapy. Fortunately, with the addition of daratumumab to CyBorD, only ~20% of patients fail to meet a VGPR. For select patients with a hematologic VGPR a therapy modification, to pursue deeper response, may be beneficial though this population is difficult to define. Autologous transplant for patients deemed appropriate at a center with experience with the AL population is ideal if can be conducted timely. Often alternative systemic therapy is pursued in the short term if there is a delay in HDT-AuSCT or the patient is not thought a good candidate based on risks (typically patients with advanced cardiac involvement). Options for alternative therapies in this setting are similar to those for patients with relapsed amyloidosis. We note data showing that for patients with cardiac AL, organ deterioration is preceded by an increase in dFLC in >90% of patients.⁽⁴⁵⁾ There is some variance in practice as to which patients should change therapy with early hematologic progression, typically defined as an increase in dFLC of 20% and an absolute value of dFLC of >20 mg/L. However, many agree for patients with a history of advanced cardiac amyloid involvement

that early salvage treatment prior to organ deterioration is necessary.⁽⁴⁶⁾ Data from the Mayo Clinic evaluating the timing of second line therapy following HDT-AuSCT showed that in 235 patients, the median time to second line therapy was 24 months and the median dFLC when restarting therapy was 99 mg/L.⁽⁴⁷⁾ Of patients proceeding to receive second line therapy, 63% had met criteria for organ progression and it was found that organ progression at the time of second line therapy was associated with inferior survival. Our practice supports this experience and aims for therapy modification or retreatment if signs of early hematologic dFLC progression for patients previously obtaining VGPR or deeper response to prior line therapy, or who fail to achieve a VGPR, particularly those with cardiac or hepatic AL involvement.

Lenalidomide based salvage or second line therapy has shown to be effective multiple series. In a series of 24 patients who had received a median of 3 lines of prior therapy, including ~70% of patients who were refractory to prior thalidomide, lenalidomide induced partial hematologic responses in 41% of patients.⁽⁴⁸⁾ While lenalidomide use in patients with AL, particularly those with cardiac involvement, has raised concerns regarding tolerability and potential obfuscation of NT-proBNP changes, it has been shown to be well tolerated when typically started at a low dose of 5 mg in combination with bortezomib and dexamethasone.⁽⁴⁹⁾ Perhaps the best experience in previously treated AL comes from the recently published phase III TOURMALINE-AL1 study which compared the combination of ixazomib and dexamethasone to an arm of physician's choice therapy which was lenalidomide and dexamethasone in the majority of patients.⁽⁵⁰⁾ There was no significant difference in the primary endpoint of overall hematologic response between the two arms (53% vs 51%). However, clinically significant secondary endpoints including median time to organ deterioration or mortality, as well as duration of therapy favored the ixazomib arm with an acceptable tolerability profile. Subsequently, data on the combination of ixazomib with lenalidomide and dexamethasone has been reported in 40 patients with relapsed AL amyloidosis showing an overall hematologic response rate of ~60%, with 41% of patients obtaining a VGPR or CR.⁽⁵¹⁾ Among these VGPR or CR obtaining patients, median progression-free survival was an encouraging 29 months. For patients in need of salvage or second line therapy who are naïve to lenalidomide and have already had an anti-CD38 targeting antibody such as daratumumab, we typically favor a lenalidomide containing regimen, typically in combination with bortezomib or ixazomib and dexamethasone.

What may change in the future?

The large structural chromosomal translocation t(11;14) is found to be over-represented in the plasma cell neoplasm underlying AL compared to multiple myeloma, with a prevalence of ~40-50%.^(52, 53) Both historical series and subgroup analysis from the *ANDROMEDA* study confirm, inferior rates of deep hematologic responses in t(11;14) patients treated with bortezomib based regimens in the absence of daratumumab.⁽⁵⁴⁾ In the *ANDROMEDA* study ~40% of patients in each arm had t(11;14). Comparing just the CyBorD treated patients with and without t(11;14) in this study, showed 12% vs 24% of patients obtained a hematologic CR, with inferior response rates for t(11;14) patients. Fortunately, with the addition of daratumumab to CyBorD rates of hematologic CR were similar and superior to CyBorD alone in patients with and without t(11;14) (59% versus 61%). However, for patients with t(11;14) and

previously treated disease, there is evidence that targeted BCL-2 inhibitor therapies may induce deep responses though further studies are underway to confirm this benefit (*NCT04847453*, *NCT04942067*). In a retrospective series of 12 patients treated with venetoclax, seven of 8 patients who were evaluable for hematologic response obtained a hematologic CR or VGPR.⁽⁵⁵⁾ Many patients without deep response to any prior therapy who have t(11;14) are able to obtain deep hematologic response for the first time with targeted BCL-2 inhibitor therapy in our experience.

B-cell maturation antigen has proven a successful target in multiple myeloma, and studies confirm target expression in samples of plasma cells associated with AL.^(56, 57) There is great interest in the potential of BCMA targeted therapies for AL, given the lower soluble BCMA levels found in the typically more indolent and lower burden plasma cell neoplasm. Early reports of BCMA directed CAR-T cell therapy in a patient with AL and concomitant multiple myeloma, achieving complete hematologic and organ responses have been encouraging.⁽⁵⁸⁾ Ongoing studies of antibody drug conjugates (*NCT04617925*) and bispecific antibodies are in progress or planned.

Anti-amyloid fibril targeting antibody therapies continue in development at this time. While birtamimab showed early promise with organ responses in previously treated AL patients, subsequent phase III studies did not show a benefit with a composite primary endpoint of time to hospitalization or mortality.⁽⁵⁹⁻⁶¹⁾ However, a post hoc analysis of all-cause mortality showed a survival benefit in the subgroup of patients with the most advanced cardiac involvement and at highest risk of early death. Mayo stage IV patients had a survival rate of 74% vs 49% compared to placebo in the phase III VITAL study.⁽⁶¹⁾ Given this benefit, a phase III study is planned with birtamimab in this high-risk Mayo stage IV subgroup (*NCT04973137*). Additionally, development of CAEL-101, a chimeric immunoglobulin that reacts with light chain amyloid fibrils has shown early signs of efficacy and safety when combined with daratumumab and CyBorD.⁽⁶²⁾ Studies of CAEL-101 in combination with standard of care plasma cell directed therapy in Mayo stage IIIA or IIIB patients are ongoing (*NCT04512235*, *NCT04504825*).

Conclusions

Management of light chain amyloidosis continues to evolve in a path unique from multiple myeloma. Emerging data highlights the complexity of options available to these patients and need for informed management. Areas of uncertainty and potential for improvement in therapy remain, and given the rarity of the disease, an emphasis on multi-center clinical trials to guide optimal therapy remains of high importance. However, the benefit seen with the development of novel therapies such as daratumumab for this population should not be understated, as many patients are able to achieve meaningful responses that in the past have proved elusive. New targets and modalities of therapy, and improved supportive care strategies, will hopefully improve survival outcomes for even the sickest of these patients in the near future.

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