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DIAGNOSIS AND TREATMENT OF AL AMYLOIDOSIS IN 2022

Introduction

Light chain (AL) amyloidosis is a rare, progressive and typically fatal disease (when advanced) characterized by organ dysfunction secondary to deposition of misfolded fibrils of immunoglobulin light chains that are produced by clonal plasma cells or B cells.[1] Although less than 10% of AL patients qualify for CRAB criteria of symptomatic myeloma (**C**alcium elevation, **R**enal dysfunction, **A**nemia, and **B**one disease),[2] the majority of these patients have significant impairment of vital organs, such as the heart, kidney and liver. This implies that the common risk factors used for the assessment of multiple myeloma (MM) are not applicable to AL. AL amyloidosis affects 8-12 individuals per million person-years.[3,4] and its clinical presentation is variable depending on the extent and number of vital organs affected. The locations of amyloid deposits can vary among patients, thus contributing to the heterogeneity of the clinical manifestations. The heart and kidney, which are the most affected organs, can lead to renal failure, cardiomyopathy, and pericardial and pleural effusions.[1] Initial symptoms at onset are often non-specific (e.g., weight loss, fatigue). Despite advances in the diagnostic tools and treatment options, early mortality rates remain high; the expected one-year mortality is approximately 30%.[5] Unfortunately, by the time the AL diagnosis is made, and treatment is initiated, the disease has often become advanced.

The diagnosis of AL amyloidosis requires histological demonstration of amyloid deposits in biopsy tissue, followed by amyloid typing to identify the precursor protein associated with the amyloid formation.[6] The tissue source can be the involved organ by amyloid formation. However, a more accessible tissue, such as subcutaneous fat, should initially be pursued when suspicion for amyloidosis is raised.[7] Fat pad aspirate in combination with a bone marrow biopsy will yield the diagnosis in approximately 90% of patients. Congo red is the gold standard staining for recognition of amyloid deposits. Tissue stained by congo red under polarized light demonstrates apple-green birefringence, illustrating the highly organized ultrastructure of the amyloid fibrils. Once the amyloid diagnosis is established, the next step is to type and determine the precursor protein associated to fibril deposition. Several methods of typing are available. The gold standard technique is laser microdissection, followed by mass spectrometry–based proteomic analysis, which has high sensitivity and specificity.[8] Alternative typing methods include antigen-antibody–based analyses, such as immunofluorescence, immunohistochemistry, and immunogold.[9] It should be emphasized that the presence of a monoclonal protein in a patient with amyloidosis does not prove AL type[10] as monoclonal gammopathy of undetermined significance (MGUS) can be found in 30-40% of patients with either wild type or hereditary systemic transthyretin amyloidosis (ATTR).[11] Finally, the distinction between ‘localized’ and ‘systemic’ AL amyloidosis is required. The designation localized applies to AL amyloidosis in which the precursor protein is produced at the site of amyloid deposition and is typically not associated with a detectable circulating monoclonal protein in the serum or urine. The common sites of localized amyloidosis are the

tracheobronchial tree, lungs, urinary tract, skin and soft tissue, oropharynx, gastrointestinal tract, and eyes.[12,13]

Due to the protein clinical manifestations and insidious onset of the disease, indications for diagnostic testing includes a broad range of features including non-diabetic nephrotic range proteinuria, non-dilated cardiomyopathy, increased NT-pro-BNP, unexplained hepatosplenomegaly, carpal tunnel syndrome, edema, purpura, or macroglossia. Biomarkers are also essential in making the diagnosis, as well as in determining the prognosis and evaluating response to therapy. Given the significant prognostic impact of cardiac involvement with early death, several markers of cardiac injury and dysfunction have been reported.[14] Serum levels of NT-pro-BNP and cardiac troponin T (cTnT) were first found to predict survival in several cohorts of patients with AL.[15-17] They were later incorporated into the first widely used staging system for AL amyloidosis (Mayo 2004).[17] The composition and biomarker thresholds were subsequently revised and two modifications of the original score are widely accepted.[18] The European version of the 2004 Mayo system identifies patients with very high NT-pro-BNP levels as having very poor outcomes and splits stage III

into two stages (IIIa and IIIb) based on a cutoff of 8500 ng/L for the values of NT-pro-BNP. More recently, the Boston group reported on the use of BNP and troponin I (TnI) for staging.[19] BNP higher than 81 pg/mL and TnI higher than 0.1 ng/mL were used in this validated staging system.

Assessment of the monoclonal protein associated to AL amyloidosis

The screening for a monoclonal protein is done by serum and urine electrophoresis with immunofixation studies as well as serum free light chain (FLC) levels.[20] More recently at the Mayo Clinic, immunofixation has been replaced by the mass spectrometry method (Mass-Fix).[21] The Mass-Fix assay has the ability to detect M-proteins with light chain glycosylation, which has been reported to be a risk factor for progression of AL amyloidosis and other plasma cell disorders.[22] In addition, bone marrow aspiration and biopsy and fluorescence in-situ hybridization (FISH) testing are indicated and can affect treatment decisions during the disease course.

Immunophenotyping

Multidimensional flow cytometry (MFC) has emerged as a potential tool highly sensitive for the detection of aberrant plasma cells in the bone marrow. Research has demonstrated that monoclonal plasma cells >2.5% at the time of diagnosis, as detected by MFC was associated with shorter survival.[23] More recently another group developed an automated computerized algorithm to assess clonality and identified three subgroups with different survival outcomes.[24]

Cytogenetics of the aberrant plasma cells

FISH abnormalities have been detected in patients with AL amyloidosis. A study conducted in 2009[25] was one of the first to describe the utility of this approach in identifying t(11;14) as an adverse risk factor for AL. Other researchers[26] described the degree of plasma cell burden and their relationship to survival an advanced cardiac disease. Additional research has[27] further stratified patients with t(11;14) who received bortezomib and IMiD-containing regimens showing that this group had an inferior survival compared to those without this translocation. It is important to note that high risk cytogenetics seen in MM (t(4;14), t(14;16) and del17p) are not common in AL. More complex karyotype clones, however, and presence of del17p have an impact on outcomes. Gain of 1q21 has also been described as an independent adverse prognostic factor in a series of 103 AL patients treated with melphalan, dexamethasone, standard chemotherapy, and daratumumab as first-line therapy.[28]

Treatment of AL amyloidosis

The aim of treatment of AL amyloidosis is to eradicate the underlying plasma cell clone in order to rapidly reduce the production of misfolded FLC proteins, mitigate further organ damage, and improve overall survival.[29]

Supportive care

Supportive measures are key in the management of AL amyloidosis, with the goal of improving quality of life, symptoms and sustaining organ function while the plasma directed therapy takes place.[30] The main pillar of supportive care is the use of diuretics. It should be noted that, in amyloidosis, cardiac function is preload dependent, and thus, avoiding reduction of intravascular volume is fundamental. Angiotensin-converting enzyme inhibitors are usually poorly tolerated due to hypotension. Similarly, calcium channel blockers are contraindicated due to their negative inotropic effects.[31] Patients with severe neurogenic orthostatic hypotension will require therapy with midodrine and/or droxidopa to facilitate diuretic dose titration.

Intracardiac thrombi are another possible complication in AL amyloidosis despite sinus rhythm.[32] Atrial thrombus, mainly located in the right or left atrial appendages, was found by transesophageal echocardiography in 35% of patients with this disease.[33] The incidence of thromboembolism is higher in patients with atrial fibrillation in the presence of cardiac AL amyloidosis than in other more common forms of atrial fibrillation. Therefore, anticoagulation must be considered on an individualized basis counterbalancing the higher hemorrhagic risk of this population due to the potential association of

vascular amyloid deposition, factor X deficiency and liver involvement. As a general recommendation, anticoagulation should be given for any atrial arrhythmia and in patients with sinus rhythm whose echocardiography shows features of left atrial mechanical dysfunction.[34]

Further, organ transplantation should be carefully assessed by a multidisciplinary team since the risk of recurrence of amyloid in the graft and progression of fibril deposition in other organs is often observed. For instance, cardiac transplantation could be considered in young patients with isolated severe cardiac involvement where effective anti-plasma cell therapy is only expected to be delivered if organ replacement occurs. The implantation of left ventricular assist devices is technically feasible for patients with severe heart failure caused by advanced cardiac amyloidosis, but the possible benefit is unclear.[35,36]

Autologous stem cell transplantation

In clinical practice, the first question to be asked is whether an AL patient is a candidate for autologous stem cell transplantation (auto-SCT). Among eligible patients, auto-SCT is an excellent option with potential for long-term survival. There are, however, no randomized trial data to support that it is superior to conventional chemotherapy. On the contrary, a phase 3 study concluded that high dose intravenous melphalan followed by auto-SCT rescue was inferior to standard-dose melphalan plus high-dose dexamethasone (MDex) in newly diagnosed patients.[37] On an intention-to-treat (ITT) basis, the median survival for MDex was 57 months vs 22 months for the auto-SCT arm (P=0.04). However, of the 50 patients randomized to receive ASCT, only 37 actually received the planned transplant and 9 of those died within 100 days, indicating an unacceptably high (24%) treatment-related mortality (TRM) rate. In a 6-month landmark analysis, no difference in survival was noted between treatment arms, thus accounting for the survival disadvantage of ASCT to the very high TRM rate. Current clinical trials demonstrate a TRM of less than 5%,[38-40] suggesting inappropriate selection of patients in that study, which in turn limits its conclusions.

Non transplant therapies

Historically, therapy for AL amyloidosis was based on targeting the plasma cell clone and treatments that were used in MM were incorporated into the management of AL patients. Treatment should be risk-adapted, considering the severity of organ involvement, characteristic of the clone, and comorbidities and should seek to deliver the most rapid and effective therapy patients can safely tolerate.[30] Early and profound reductions of the amyloid LC are associated with the greatest chance of organ improvement and prolongation of survival outcomes.[41-43] The optimal end point of therapy is still a matter of debate. However, achievement of organ response and profound hematological response should be the long-term goal of therapy. Novel definitions of response and minimal residual disease (MRD) assessment are currently being investigated for AL.[41,44,45]

Most patients with AL amyloidosis are not eligible for auto-SCT. Melphalan with steroids has historically been the first-line approach for the treatment of AL.[46] However, given the efficacy of proteasome inhibition in MM, bortezomib was evaluated in AL amyloidosis. Real-world studies of CyBorD (cyclophsophamide, bortezomib and dexamethasone) demonstrate a need for more effective therapies for AL amyloidosis, with hematologic responses reported in 60-65%, cardiac responses in 17-32%, and renal responses in 15-25% of patients[45,47]. Encouragingly, the phase III ANDROMEDA trial showed that the addition of daratumumab to a CyBorD regimen significantly increased the rates of hematologic complete response (CR) (53% vs 18%, p<0.001), cardiac response (42% vs 22%), and renal response (53% vs 24%), with median time to hematologic CR of 60 days in the daratumumab-CyBorD group compared to 85 days in the CyBorD group (**Figure 2**)[48].

Treatment intensification with high dose melphalan is an option in a subset of patients and it has been suggested as a sequential response-driven approach for patients undergoing CyBorD who don't exhibit a satisfactory response after induction therapy.[49] In addition, a phase 3 study in intermediate risk AL patient demonstrated that bortezomib, melphalan and dexamethasone (BMD) induced a significantly higher HR rate (81% vs 57%, CR, 23% vs 20%; VGPR 42% vs 20%) than MDex, with prolonged overall survival. Cardiac and renal responses were observed in 38% and 44% of cases with BMDex and in 28% and 43% of cases with MDex, respectively.[50]

Approximately 20% of patients have advanced cardiac stage at the time of diagnosis. Treatment of these patients considered high-risk and remains an unmet need. Initially, the European collaborative study reported lower haematological response rates in patients with stage IIIb disease.[51] This is likely a reflection of very advanced cardiac disease. Further, studies have reported on the importance of rapid responses in patients with stage IIIb, demonstrating an improvement in survival for patients treated with CyBorD compared to CTD (cyclophosphamide, thalidomide and dexamethasone); but most importantly described how patients with rapid haematological response in 1-month are associated with improved survival.[52] Based on these reports, recent studies have explored the possible benefit of the substitution of dexamethasone by methylprednisolone with the aim of decreasing toxicity.[53]

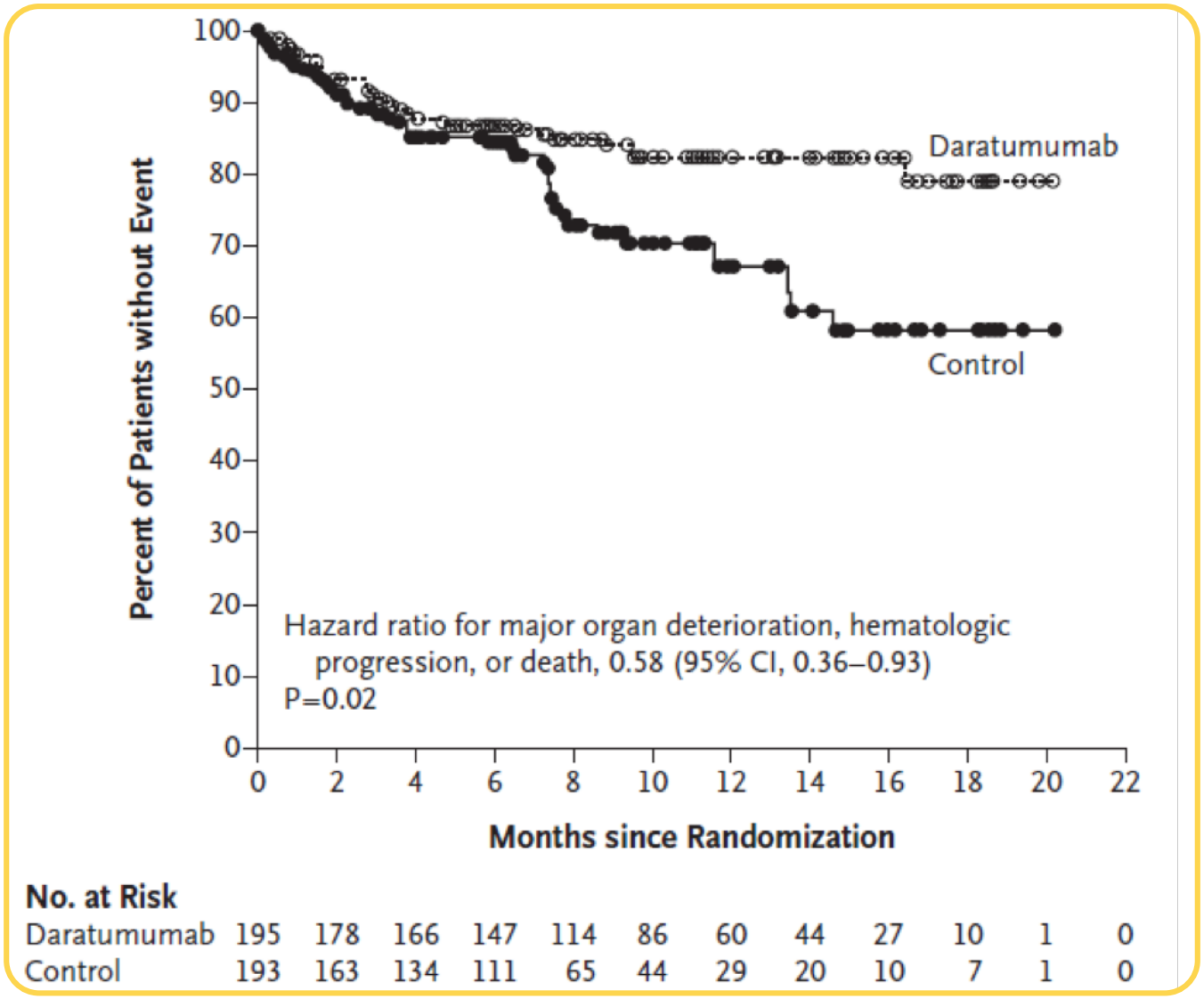

Figure 2. *Kaplan–Meier Estimates of Survival Free from Major Organ Deterioration or Hematologic Progression. Shown are the results of the Kaplan–Meier estimates of survival from major organ deterioration or hematologic progression among patients in the intention- to-treat population. Major organ deterioration was defined as end stage cardiac or renal failure; adapted from Kastritis et al, 2021*

Notably, patients treated with methylprednisolone exhibited faster responses which translated into a better survival rate (2-year OS of 65% versus 43%). Our group presented a preliminary report on the use of CyBorMe (cyclophosphamide, bortezomib and methylprednisolone) for newly diagnosed AL amyloidosis patients treated at a single referral center and compared with a historic group of patients treated with a standard CyBorD regimen used at our institution. Overall response rates (ORR) were similar among the CyBorD and CyBorMe groups (90.6% vs 100%, p=0.7). However, patients in the CyBorMe group had a faster time to first (4 vs 6 weeks) and best response compared to CyBorD (p=0.003 and 0.047, respectively). In addition, a trend towards lower dFLC after one month and higher cardiac response rate was noted (44% and 31% of patients treated with CyBorMe and CyBorD, respectively). Out of 7 evaluable cases for cardiac involvement, 3 patients exhibited cardiac response at a median of 8 weeks.[54]

Venetoclax is also an appealing option for patients with t(11;14), but few data are available to date. Although a change in AL amyloidosis therapy is typically prompted by the occurrence of hematologic or organ progression, there is growing consensus that failure to achieve an optimal response within the first few cycles of treatment should also lead to a change in therapy[55]. Given the poor prognosis of patients with suboptimal response to first-line therapy and the encouraging findings of these studies, further research is warranted to identify the optimal timing of response assessment and to better understand the role for early switch to second-line therapy in AL amyloidosis.

Anti-fibril directed therapy

Treatment of AL amyloidosis has been directed at reducing the circulating precursor LC's by targeting the malignant B-cell clone. Recently, two anti-amyloid antibodies have been tested in clinical trials for AL amyloidosis, but despite encouraging preliminary results, further clinical studies were discontinued due to futility or unfavorable toxicity.[56,57] Recently, CAEL-101, a monoclonal antibody that reacts with a conformational epitope present on partially denatured and fibrillar LC's was investigated in phase1a/b study. All patients were exposed to 1 to 10 lines of therapy, and median times from last chemotherapy administration were 2.6 and 7.4 months in the phase 1a and 1b portions of the study. Twenty patients (74%) demonstrated VGPR at the time of first infusion of CAEL-101. Fifteen of 24 patients (63%) had a therapeutic response to CAEL-101 as evidenced by serum biomarkers or objective imaging modalities with a median time of response of 3 weeks.[58] This study provides rationale for the development of a phase 3 clinical trial program for patients with AL amyloidosis with stage IIIa and IIIB that are randomized to CAEL-101 plus CyBorD or CyBorD alone.

Conclusion

AL amyloidosis is a rare disease often associated with devastating outcomes due to advanced cardiac disease. As delays in the diagnosis of AL amyloidosis are common, finding biomarkers that could potentially help us diagnose this entity is crucial. Recently, CyBorD plus daratumumab was approved by FDA and Health Canada becoming the first and only treatment approved for patients with newly diagnosed AL amyloidosis. Based on this exciting approval more work is needed to improve awareness and advance research that could potentially lead to early diagnosis and innovative use of novel drug combinations.

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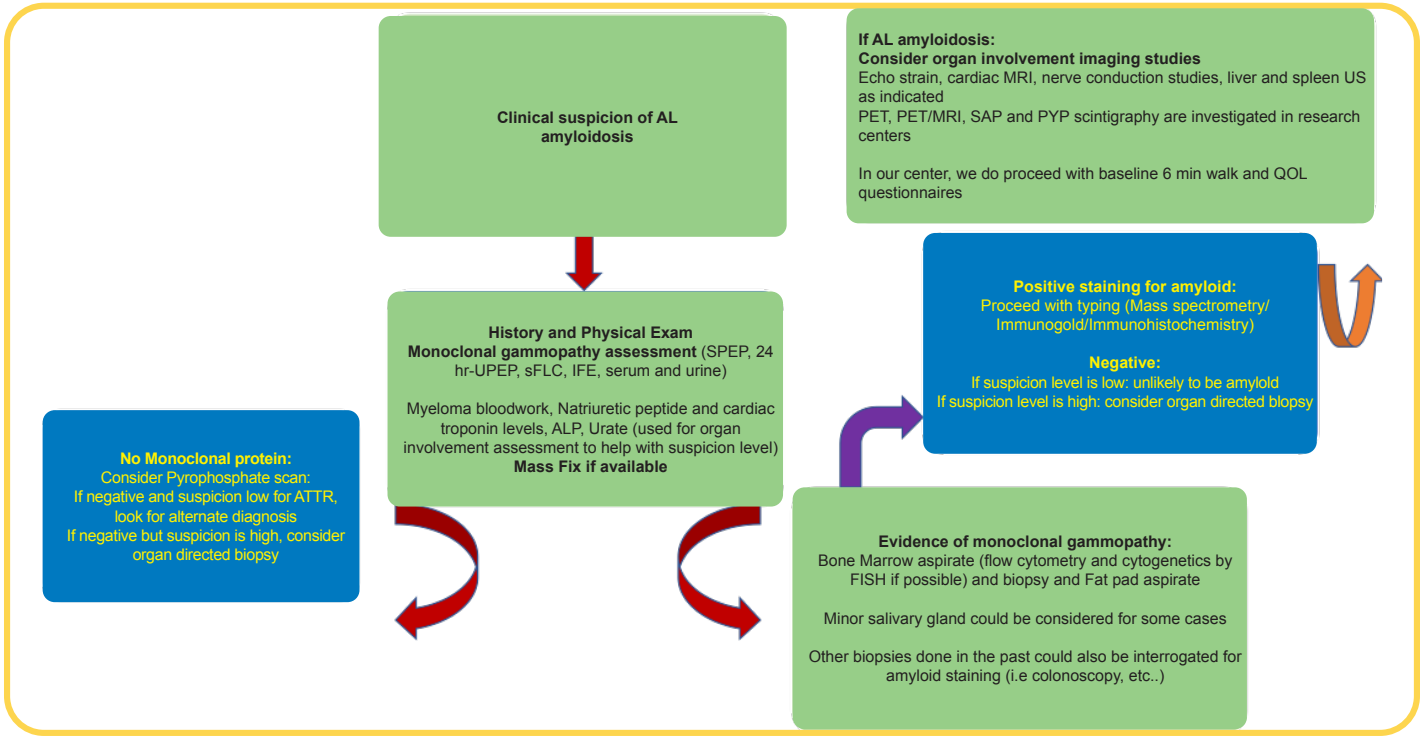

Figure 1. *Diagnostic algorithm for AL Amyloidosis; courtesy of Victor Zepeda, MD*

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