Amiloidosi da catene leggere: approccio clinico

In depth review

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ABSTRACT
L'amiloidosi da catene leggere è una malattia progressiva che può determinare disfunzione multiorgano potenzialmente fatale. Vi è stato grande progresso nella stadiazione della malattia, nella valutazione della risposta e nelle strategie di trattamento. Il fattore chiave per un migliore survival è una diagnosi precoce, che però può essere difficoltosa visti i sintomi spesso aspecifici facilmente riconducibili a condizioni più comuni. Una volta confermata la diagnosi sono disponibili sistemi di stadiazione per ottenere una prognosi in relazione all'overall-survival e al survival renale. Sono stati sviluppati criteri nefrologici ed ematologici di risposta terapia per massimizzare la risposta terapeutica e minimizzare gli effetti avversi. Sono in corso di sviluppo in trial clinici nuove terapie, specialmente anti-fibrillari. Per i pazienti che hanno dimostrato una buona risposta al trattamento, il trapianto renale può essere un'opzione se l'insufficienza renale non si è risolta.

PAROLE CHIAVE: amiloidosi, amiloidosi da catene leggere, catene leggere, trapianto renale

Introduction

Immunoglobulin Light Chain Amyloidosis (AL) is a progressive and debilitating disease with multiorgan complications and increased mortality [1]. This disease is characterized by misfolding of the variable region of light chains leading to fibril formation and deposition in organs, most commonly in the kidneys [2]. The key to improving survival and quality of life is early diagnosis as median overall survival (OS) of patients diagnosed with stage I vs stage IV AL using the Mayo 2012 model is 94.1 months vs 5.8 months respectively [3]. In this manuscript, our aim is to discuss the key diagnostic approaches and therapeutic options for this complex disorder. For more in-depth discussion, please refer to the references provided.

Diagnosis

The diagnosis of AL can often be delayed as patients may have multiple nonspecific symptoms. The median time to diagnosis from symptom onset can be up to 2.7 years [4]. In a patient survey, nearly 50% of the patients saw more than 3 doctors before their diagnosis was made [5]. These are concerning statistics considering the prognosis worsens as the stage of disease increases [3, 6]. Unfortunately, symptoms are often nonspecific such as fatigue, weight loss, constipation or diarrhea, edema and shortness of breath [7]. The key is extrarenal involvement which is uncommon in other glomerular disease. Symptoms such as orthostasis, unexplained improvement in hypertension, heart failure, new onset peripheral neuropathy, carpal tunnel syndrome, easy bruisability, when accompanied by proteinuria or renal impairment, should prompt a workup for AL [8]. Diagnostic workup should begin with serum protein electrophoresis and serum free light chains (sFLC), urine protein electrophoresis and a bone marrow biopsy if indicated. However, the diagnosis of amyloidosis requires demonstration of amyloid deposits in tissue, preferably the affected organ, but surrogate sites can be used instead [8]. Once amyloid has been identified, typing is required in order to prescribe the proper treatment [9]. Typing can often be done by immunofluorescence or immunohistochemistry in the kidney but proteomics by mass spectrometry is the gold standard [10].

Staging

Staging is crucial to estimating the morbidity and mortality implications of the patient. There are multiple staging systems that have been developed [11]. Majority of the staging systems focus on the overall survival of the patients. These typically involve cardiac assessment using biomarkers such as cardiac troponin and brain natriuretic peptide (BNP); the most commonly used is N-terminal pro b-type natriuretic peptide (NTproBNP). The first model now known as Mayo 2004 amyloid staging system uses cardiac troponin T and NTproBNP to establish a 3-stage prognosis model where stage 1 denotes normal troponin T and NTproBNP, stage 2 is when one of the laboratory values is abnormal and stage 3 is when both have exceeded the cutoff [12]. The cutoffs for troponin T and NT-proBNP are < 0.035 ng/mL and < 332 pg/mL respectively for this model. This model has been modified by the European Collaborative studies which divides stage 3 into 3a (NTproBNP > 332 and < 8500 pg/mL) and 3b (NTproBNP > 8500 pg/mL) [13]. Mayo 2004 was later replaced with the Mayo 2012 amyloid staging system which increases the stages to 4 by incorporating the difference between involved to uninvolved free light chain (dFLC) < 180 mg/L along with troponin T < 0.025 ng/mL, NT-proBNP < 1800 pg/mL [3]. Other variations include systolic blood pressure [14] and the use of troponin I and BNP [15]. These models all showed the ability to prognosticate OS based on simple and reproducible laboratory tests. More importantly, these models help predict treatment related mortality to therapy such as autologous stem cell transplantation (ASCT) which allows for better patient selection and improved outcomes [16, 17]. In addition to prognostic models for OS,

prognostic models have also been developed for the kidney. The Palladini model uses proteinuria (< 5 g/d) and eGFR (< 50 ml/min/1.73m^2) to predict kidney survival [18]. Patients with stage 1 have a 0-4% chances of end stage renal disease (ESRD) vs 60-85% for stage 3 patients at 3 years. The Kastritis model uses proteinuria to eGFR ratio to separate patients by those with a ratio of < 30, 30-99 and > 100. Dialysis rate of stage 1, 2, and 3 patients were 0%, 9%, 35% respectively [19]. Like the OS prognostic models, renal prognostic models are used to adjust therapy. In particularly those with Palladini stage 3 and an eGFR of < 20 ml/min/1.73 m^2, a hematologic response of very good partial response (VGPR) must be reached within 3 months or else the chance of renal recovery diminishes rapidly.

Response Assessment

One of the most important advances in the treatment of AL is the improvement in response assessment. The original hematologic response criteria for AL had complete response (CR), partial response (PR) stable disease and progression [20]. PR was defined as > 50% reduction of the serum or urine monoclonal (M) protein. Since these guidelines preceded the introduction of sFLC in clinical practice, the reduction of M-protein was mainly from M spike measured by serum protein electrophoresis. Since AL is most often the result of immunoglobulin light chain, sFLC was found to be a much better marker [21]. After its introduction, sFLC became the main determinant of hematologic response [22]. CR is now defined as a lack of detectable M-protein and a normal kappa to lambda sFLC ratio while an additional category of VGPR was added defined as a dFLC of < 40 mg/L [6]. PR was > 50% reduction of the dFLC. Multiple studies have found that VGPR is the minimum hematologic response required for renal response to occur and improved OS. As our ability to measure deeper response improve, so has our response criteria [18, 19, 23, 24]. Recently, a dFLC of < 10 mg/L or involved FLC of < 20 mg/L have been found to produce superior results in organ responses and OS as compared to VGPR or CR [25]. With minimal residue disease (MRD) now becoming routinely used in multiple myeloma response assessment [26], MRD by next generation flow cytometry has also been evaluated in AL patients. So far, the results are less consistent than those from multiple myeloma. OS and renal response of MRD negative patients were improved in some studies but not in others [27-30]. However, the differences in outcomes may have been due to the differences in methodology, thus further studies are needed to establish the role of MRD assessment by next generation flow cytometry in AL. MRD like assessment can also be accomplished by mass spectrometry measurement of monoclonal immunoglobulin light chains (mass fix) [31]. In a small study, patients who are in CR and MRD negative by next generation flow cytometry, those who were also negative by mass fix had a better outcome than patients who were mass fix positive. If confirmed, mass fix could be a very useful tool in gauging response since it is easier to perform than a bone marrow biopsy [32].

Clone Directed Therapy

The first effective treatment for AL was a combination of melphalan and prednisone. In the seminal paper from 1997, Kyle et al reported a median survival of 18 months with oral melphalan and prednisone versus 8.5 months with colchicine alone [33]. This was actually a major improvement at the time; however, the median survival was still less than two years. High dose dexamethasone achieved a median OS of 31 month in a small trial, but its toxicities made it less tolerable [34]. The next major advance was the introduction of ASCT. It produced a median OS of 4.6 years which was even higher in patients without cardiac involvement [35]. These results came at a high cost as the treatment related mortality can be over 40% especially in high-risk patients [36]. This high

treatment related mortality was the main reason ASCT was found to be inferior to melphalan dexamethasone in a randomized trial [37]. Two small studies found bortezomib, cyclophosphamide, and dexamethasone (CyBorD) was capable of achieving very high hematologic response rates of 81-94% which was very exciting, but real-world data suggested a hematologic rate was closer to 60% [13, 38, 39]. Nevertheless, it was well tolerated making it the therapy of choice in the frontline setting. This however provided the backbone therapy that led to the landmark 2021 phase 3 open label trial ANDROMEDA, where patients were randomized to standard of care with six cycles of CyBorD OR standard of care plus daratumumab followed by 18 cycles of daratumumab maintenance [40]. Daratumumab is an IgG-Kappa monoclonal antibody directed towards CD-38 cell surface glycoprotein found on plasma cells. The addition of daratumumab to CyBorD improved overall hematologic response at 6 months from 76.7% in CyBorD alone to 91.8%, VGPR or better from 49.2% to 78.5%, cardiac response from 22.2% to 41.2% vs 22.2%. Renal response also improved from 23.9% in CyBorD to 53.0% with Daratumumab CyBorD. The treatment group had a significantly higher and faster complete response (median time 60 days vs 80 days in control), and longer survival free from hematological progression or organ deterioration. It appears to have overcome the negative prognostic effect of t(11;14) which in the past required ASCT to overcome. As a result of these extraordinary results, daratumumab CyBorD has become the standard of care for frontline therapy for AL patients.

Second Line Therapy and Beyond

Immunomodulators (IMiD) which include thalidomide, lenalidomide and pomalidomide have also been shown to have some positive benefits in AL. Cyclophosphamide thalidomide dexamethasone (CTD) had been used in the frontline setting in AL but in a retrospective matched comparison, CTD was found to be inferior to CyBorD in terms of CR rate (24.6% vs 40.5% respectively) and progression free survival (14 months vs 28 months respectively) [41]. Lenalidomide dexamethasone has been shown to have an overall response rate of 67% and 44.5 months of progression-free survival, but tolerability was an issue with a high dropout rate [42]. In a retrospective study comparing lenalidomide dexamethasone vs full dose bortezomib dexamethasone and risk adjusted bortezomib dexamethasone was found that hematologic response rates were better with bortezomib dexamethasone (full dose vs risk adjusted) regimens (76% and 77%, respectively) compared to 58%; CR rates were 38% and 40%, respectively, compared to 14%. However, the risk-adjusted bortezomib regimen had the best 1-year OS of 81% vs 56% in full dose bortezomib regimen and 53% in lenalidomide based therapy ($p = 0.05$) [43]. More recently, a phase II trial with pomalidomide with dexamethasone produced a hematologic response of 68% and a renal response of 17% [44]. Given the poorer tolerability of IMiDs, they are generally used as rescue therapies during relapse rather than frontline treatment. Venetoclax, a BCL-2 inhibitor approved for treatment of chronic lymphocytic leukemia has been found to be active in multiple myeloma with t(11;14) abnormality [45]. AL patient with t(11;14) abnormality also responds to venetoclax which is exciting since t(11;14) is negative prognostic marker for AL [46-48]. Belantamab, an antibody conjugate drug targeting B-cell maturation antigen (BCMA) has been reported to have a high rate of response in patients with relapsed refractory multiple myeloma and AL in small studies [49, 50]. Unfortunately, belantamab is currently not available in the United States awaiting further studies.

Non-Clone Directed Therapy

Most therapies in AL focus on killing the clone that is producing the amyloidogenic light chain. While these therapies stop the production of the toxic light chains, the amyloid already deposited is

untouched. Experimental models have shown the monoclonal antibody 11-1F4 can expedite the dissolution of lambda and Kappa AL amyloidosis in mice [51]. In Phase 1a/1b studies, 15 out of 24 (63%) patients with cardiac, hepatic, GI, soft tissue or renal involvement treated with 11-1F4 had an organ response most notably in cardiac patients with 67% response rate [52]. These encouraging results prompted a phase III randomized controlled multicenter study NCT04504825 that is currently enrolling. Another monoclonal antibody, birtamimab, formally known as NEOD001 has also demonstrated activity in a Phase II (PRONTO) study but did not reach primary outcome in a phase III (VITAL) study [53]. However, in a post hoc analysis, a survival benefit was found in Mayo stage IV patients [54]. A new phase III trial, NCT04973137, is currently enrolling to confirm these results.

Kidney Transplantation

It is well appreciated that kidney survival worsens over time in AL with 34% of patients progressing to ESRD at a median time of 18 months [55]. It is also known that AL patients with ESRD have a significantly inferior survival as compared to non-AL patients. Single center studies report median survival of 10.4 to 39 months after starting dialysis in these patients [55, 56]. This is similar to the results from a study of the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry that found the median survival of patients with amyloidosis was 2.08 years compared to 6.0 years for non-amyloidosis patients [57]. Renal replacement therapy with kidney transplantation would seem like a better option but it is not without risk. Early experience showed higher mortality in patients with AL secondary to infection, cardiac causes and amyloidosis [58]. Selecting the ideal candidate for kidney transplantation is crucial for a successful outcome. Recently, in a multicenter study of AL patients undergoing kidney transplant, the median OS of those with VGPR or better was 8.6 years compared to 6.8 years with less of a hematologic response. Median graft survival was 7.8 years, which was also superior in the VGPR or better group, but MRD was not assessed in this study. Patients with CR had a longer time to recurrence, but this did not affect renal allograft outcome. Treatment of the AL can also start after the kidney transplant as long as a VGPR or better hematologic response can be attained [59]. Clonal control and cardiac involvement are the two big additional factors to consider when evaluating AL patients for kidney transplantation [59, 60].

Conclusion

AL is a complex multisystem disease which used to carry a grim prognosis. With early diagnosis and improved upfront treatment with daratumumab and CyBorD, the outcomes have improved significantly. VGPR has now been established as the minimum hematologic response required for organ responses and improved survival; however, deeper response such as MRD negativity may prove to be even better. Kidney transplantation is an option for selected patients who had achieved clonal control and are fit enough from a cardiac standpoint. In the future, anti-fibril therapies may enhance organ response to clone directed therapy thus improving organ survival and OS. It is also important to mention that supportive care with diuretics, adrenergic agonist to increase blood pressure, cardiac supportive care with anti-arrhythmic medications and defibrillators are important adjuvant therapies to maintain the wellbeing of the patients while the clone direct therapy is working. On the other hand, there is no role for beta blockers and ACE inhibitors as they are generally poorly tolerated in these patients [61, 62]. The advancement in AL has made this once a rapidly fatal disease to one that can be managed with the proper team of clinicians managing all of the different parts of this disease.

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