Chinese consensus on the diagnosis and treatment of immunoglobulin light-chain cardiac amyloidosis

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Epidemiology of Amyloid Light-Chain Cardiac Amyloidosis (AL-CA)

The annual incidence of amyloid light-chain (AL) amyloidosis is 3–5/million, and the incidence in men is slightly higher than that in women. Approximately, 70% of patients with newly diagnosed AL amyloidosis have cardiac involvement.

The Diagnosis of AL-CA

Clinical manifestations of AL-CA

Cardiac amyloidosis (CA) is a major cause of restricted cardiomyopathy or heart failure with preserved ejection fraction, characterized by exertional dyspnea and right heart failure. In addition, patients may have atrial fibrillation, conduction block, and other arrhythmias. In the advanced stage of the disease, refractory hypotension and syncope may occur.[1]

Examinations for AL-CA

Electrocardiography (ECG): The typical ECG features of AL-CA are low voltage in limb leads[1] and Q-waves and poor R-wave voltage increments in leads V1–V3.

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Serum biomarkers: B-type natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-pro-BNP), and cardiac troponin T/I (cTnT/I) are biomarkers which are used to evaluate the severity of CA and are related to prognosis.[1]

Echocardiography: Echocardiography is the first-line screening method for CA. The findings are as follows. (1) The thicknesses of the interventricular septum and left ventricular posterior wall are ≥12 mm.[1] (2) The echogenicity of the myocardium has a brilliantly speckled appearance. (3) The size of both ventricles decreases, and the size of both atria increases. (4) The mitral filling pattern is abnormal, especially at later stages. (5) The left

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ventricular ejection fraction (LVEF) at the early stage is normal but then decreases rapidly. Strain demonstrates not only a reduction in longitudinal contraction but also a reduction in longitudinal strain that predominantly affects the basal segments with sparing of the apical segments, which gives rise to the typical appearance of a "bull's eye pattern". However, these changes in echocardiography cannot differentiate AL-CA from transthyretin cardiac amyloidosis (ATTR-CA).

Cardiac magnetic resonance (CMR): The characteristic pattern of AL-CA is diffuse subendocardial late gadolinium enhancement (LGE).[1] The LGE distribution of AL-CA is not consistent with the blood supply area of coronary arteries; so, it can be distinguished from ischemic cardiomyopathy. In terms of special parameters, AL-CA patients can have an elevated native T1 and extracellular volume (ECV) on T1 mapping sequences. Native T1 in AL-CA is usually higher than that in ATTR-CA; ECV in ATTR-CA is usually higher than that in AL-CA. However, the parameters in different types of CA can overlap, and it is difficult to distinguish the type of CA solely according to CMR. For prognosis evaluation, the range of LGE and elevation of ECV can be used to predict the mortality risk of AL-CA. During follow-up, narrowing of the area of LGE and a reduction in ECV indicate a reduction in amyloid fibril load.

Positron emission tomography (PET): ^{11}C-Pittsburgh compound B, ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol are imaging tracers that can reversibly combine with the β-sheet structure of amyloid fibrils, resulting in abnormal concentrations in the deposition site of amyloid fibrils. This can help us to determine whether the heart and other organs are involved. At present, the main parameters of interest are the retention index and standardized uptake value ratio of the heart and blood pool. Several studies with small sample sizes suggest that amyloid can be quantitatively evaluated by tracer concentration with dynamic observation and dynamic metabolic parameter analysis, which can also be used for risk stratification and follow-up.

Tissue biopsy

The presence of Congo red-positive deposits of amorphous material on biopsy is the gold standard for the diagnosis of amyloidosis. Biopsy of involved organs (heart, kidney, and liver) has a high positive diagnostic rate. For patients who are not candidates for organ biopsy, abdominal fat, tongue, and bone marrow biopsy can be performed. In addition, amyloid fibers show a disorderly arrangement of unbranched fiber structures with a diameter of 7–14 nm under an electron microscope, which can be used as a complementary diagnostic means.

Typing of AL-CA

Detection of monoclonal immunoglobulin in the serum and urine: Almost all patients with AL-CA have monoclonal immunoglobulins. Serum protein electrophoresis, blood/urine immunofixation electrophoresis, and serum free light-chain (sFLC) should be combined to detect monoclonal immunoglobulin.

Identication of light chains in amyloid substances: (1) Antibody-based immunohistochemistry, immunofluorescence, and immunoelectron microscopy methods rely on commercial antibodies. However, they may show false-negative results when amyloidogenic protein epitopes are unavailable or individual differences in conformation are present. False-positive results may appear when there is serum protein contamination. (2) For mass spectrometry-based proteomics analysis, laser microdissection of paraffin-embedded sections and mass spectrometry-based proteomics can identify amyloidogenic proteins, establishing the currently recognized gold standard.

The diagnostic criteria of AL-CA

The diagnosis of AL-CA needs to meet the following (1) + (2) + (3) conditions and at least one of (4) or (5): (1) Typical clinical manifestations or imaging characteristics of AL-CA; (2) Monoclonal immunoglobulin in the serum or/and urine;[2] (3) The tissue biopsy of myocardium or other parts exhibits deposition of amorphous material that is Congo red positive under polarizing light microscopy or non-branching fiber with a diameter of 7–14 nm under an electron microscope; (4) The amyloidogenic protein component is proven to be immunoglobulin light chain based on immunohistochemistry, immunofluorescence, immune-electron microscopy or mass spectrometry;[1] (5) A ^{99m}Tc-labeled pyrophosphate (^{99m}Tc-PYP) scan of the heart is negative.

The differential diagnosis of AL-CA is shown in Supplementary Material, http://links.lww.com/CM9/B882 and the diagnostic flow chart of AL-CA is shown in Supplementary Figure 1, http://links.lww.com/CM9/B882.

Prognostic Staging of AL-CA

For the prognostic staging of AL-CA, Mayo 2004 staging and Mayo 2012 staging were adopted.[2,3] The majority of patients with AL-CA can be classified as Mayo 2004 stage II or III [Supplementary Table 1, http://links.lww.com/CM9/B882].

Treatment of AL-CA

Therapeutic goal

The ideal therapeutic goal of AL-CA is to achieve complete cardiac remission. However, available treatments target clonal plasma cells to reduce serum monoclonal immunoglobulin levels and achieve cardiac remission through the body's self-clearance mechanism. Therefore, the goal of AL-CA treatment is high-quality hematological remission (at least very good partial response [VGPR] and above). Cardiac response usually occurs within 3–12 months after hematological remission. Patients with AL-CA can benefit from a better hematological response, including a stringent difference between involved and uninvolved serum free light chains (dFLC)

response (dFLC <10 mg/L), involved FLC <20 mg/L, negative minimal residual disease, and so on.

Principles of treatment

(1) The key treatment for AL-CA is anti-plasma cell therapy. (2) Supportive treatment is very important, including heart transplantation in end-stage patients. (3) If one cycle of first-line chemotherapy fails to achieve hematological partial remission or ≥VGPR is not achieved within three cycles, the treatment scheme is recommended to be changed. (4) The efficacy should be consolidated with an extra 3–4 cycles after achieving ≥VGPR. (5) There is no evidence to support maintenance therapy.

First-line treatment

Daratumumab: (1) Because daratumumab can induce a rapid and deep hematological response, it is recommended as the first-line therapy.[2] Recommended regimens include daratumumab plus bortezomib/dexamethasone (BD), daratumumab plus bortezomib/cyclophosphamide/dexamethasone,[4] and daratumumab plus dexamethasone. (2) Daratumumab should be administered intravenously at a dose of 16 mg/kg of body weight or at a fixed dose of 800 mg for 28-day courses, once weekly for 1–2, once biweekly for cycles 3–6, and then once every 4 weeks. The subcutaneous form is administered at a fixed dose of 1800 mg, and the frequency is the same as the intravenous form. Twelve or more cycles of daratumumab are recommended.

Chemotherapy based on bortezomib: (1) If daratumumab cannot be applied as a first-line therapy, bortezomib-based therapy should be considered, including bortezomib/cyclophosphamide/dexamethasone, bortezomib/melphalan/dexamethasone (BMD) and BD. BMD is suitable for patients with t(11;14). BD is indicated for Mayo 2004 stage III patients with poor general condition. (2) Bortezomib is recommended at a dose of 1.3 mg/m^2 subcutaneously once a week. The dose of dexamethasone is typically 160 mg/cycle but can be reduced to 40–80 mg/cycle in patients at Mayo 2004 stage III.

Chemotherapy based on melphalan: (1) Melphalan combined with dexamethasone has a relatively slow onset of action and is indicated for patients who cannot tolerate or afford bortezomib or daratumumab. (2) Melphalan is recommended at a dose of 8–10 mg·m^{-2}·day^{-1} on days 1–4. Dexamethasone is recommended at a dose of 20–40 mg/day on days 1–4. Treatment of relapsed and refractory AL-CA is shown in Supplementary Material, http://links.lww.com/CM9/B882.

Supportive treatment

Volume management: Volume management is an important part of AL-CA management. For diuretics, loop diuretics and spironolactone should be applied. Tolvaptan is recommended for patients with poor response to conventional diuretics, hyponatremia, or renal dysfunction.

Other drugs for the treatment of heart failure: Other drugs, including angiotensin system inhibitors, sacubitril-valsartan, β-blockers and digitalis, do not improve the prognosis of patients with AL-CA and even worsen hypotension or ventricular arrhythmias in them.

Arrhythmia: AL-CA patients can have tachyarrhythmia and bradyarrhythmia. When combined with atrial fibrillation/flutter, anticoagulant therapy is recommended regardless of the CHA2DS2-VASc score. Digoxin is contraindicated for ventricular rate control because it can bind to amyloid fibers and cause digitalis toxicity. Amiodarone is preferred for rhythm and heart rate control. Implantable cardioverter defibrillator therapy is feasible for patients with sudden cardiac death after resuscitation or CA combined with persistent ventricular tachycardia if the expected survival duration is >1 year. Although such treatment may be effective for ventricular arrhythmias, it does not prolong the survival of CA patients because the main cause of death in CA patients is electromechanical dissociation. Pacemakers can be implanted in AL-CA patients with atrioventricular block if indicated. The efficacy and prognostic benefits of cardiac resynchronization therapy (CRT) in patients with AL-CA are still unclear.

Others: For young patients with high-risk AL-CA, heart transplantation is feasible, followed by chemotherapy or autologous stem cell transplantation.

Drugs targeting amyloid deposits

Randomized controlled studies have shown that doxycycline is ineffective for AL-CA.[5] CAEL-101 is a monoclonal antibody targeting the conformational epitope of light-chain amyloid fibrils. A phase III clinical trial of CAEL-101 is currently underway. Therapeutic effect criteria and follow-up are shown in Supplementary Material, http://links.lww.com/CM9/B882.

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Conflicts of interest

None.

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