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Report of Consensus Panel 6 from the 11 th International Workshop on Waldenström's Macroglobulinemia on Management of Waldenström's Macroglobulinemia Related Amyloidosis

Giampaolo Merlini[a,*], Shayna Sarosiek[b], Giulia Benevolo[c], Xinxin Cao[d], Meletios Dimopoulos[e], Ramon Garcia-Sanz[f], Moshe E. Gatt[g], Carlos Fernandez de Larrea[h], Jesus San-Miguel[i], Steven P. Treon[b], Monique C. Minnema[j]

[a] *Amyloidosis Research and Treatment Center, IRCCS Policlinico San Matteo, and University of Pavia, Pavia, Italy*
[b] *Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*
[c] *SSD Mieloma Unit e Clinical Trial e S.C. Hematology U, Turin, Turin, Italy*
[d] *Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, Beijing, China*
[e] *Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*
[f] *Hematology Department, University Hospital of Salamanca, Research Biomedical Institute of Salamanca, CIBERONC and Center for Cancer Research-IBMCC (University of Salamanca-CSIC), Salamanca, Salamanca, Spain*
[g] *Department of Hematology, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*
[h] *Hospital Clínic de Barcelona, IDIBAPS Universitat de Barcelona, Barcelona, Spain*
[i] *Clínica Universidad de Navarra, Centro de Investigación Médica Aplicada, Instituto de Investigación Sanitaria de Navarra, Centro de Investigación Biomédica en Red Cáncer, Pamplona, Navarra, Spain*
[j] *Department of Hematology, University Medical Center Utrecht, Utrecht, Utrecht, the Netherlands*

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ABSTRACT

Consensus Panel 6 (CP6) of the 11th International Workshop on Waldenström's Macroglobulinemia (IWWM-11) was tasked with reviewing the state of the art for diagnosis, prognosis, and therapy of AL amyloidosis associated with Waldenström macroglobulinemia (WM). Since significant advances have been made in the management of AL amyloidosis an update for this rare disease associated with WM was necessary. The key recommendations from IWWM-11 CP6 included: (1) The need to improve the diagnostic process by recognizing red flags and using biomarkers and imaging; (2) The essential tests for appropriate workup; (3) The diagnostic flowchart, including mandatory amyloid typing, that improves the differential diagnosis with transthyretin amyloidosis; (4) Criteria for therapy response assessment; (5) State of the art of the treatment including therapy of wild type transthyretin amyloidosis associated with WM.

Introduction

Amyloidosis is a complex medical disorder characterized by the production, misfolding, and accumulation of fibrillary deposits of pathogenic proteins. Patients with Waldenström macroglobulinemia (WM) are at risk for developing amyloidosis, including immunoglobulin light chain (AL) amyloidosis and the seemingly unrelated but potentially coexistent transthyretin (ATTR) amyloidosis. The process of amyloid formation can lead to significant life-threatening organ dysfunction unless the disease is promptly recognized and appropriate, and effective therapy is rapidly instituted. WM-associated AL amyloidosis develops in about 7.5% of patients with WM [1]. The most common organs affected in these patients include the kidneys, heart, nerves, lung, and lymph nodes. Due to the propensity for organ dysfunction, distinct differences exist in the monitoring, diagnostic approach, and management of these patients compared to those with only WM or with a non-IgM-related AL amyloidosis. WM-associated AL amyloidosis is a rare condition and therefore no large, high-quality trials are available to guide treatment decisions. Recommendations for monitoring and treatment of these patients are based on case series, retrospective reviews, and expertise from large academic centers.

During the 11th International Workshop on Waldenström's Macroglobulinemia, there was a lively discussion on the management of AL amyloidosis associated with WM, and the key questions debated are reported below.

* Corresponding author: Giampaolo Merlini, MD Amyloidosis Research and Treatment Center IRCCS Policlinico San Matteo, Viale Golgi 19, 27100 Pavia, Italy.
E-mail address: gmerlini@unipv.it (G. Merlini).

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Table 1
Red flags for systemic amyloidosis.

Red flags
• Fatigue and weight loss
• Macroglossia
• Periorbital purpura
• History of bilateral carpal tunnel syndrome
• Symptoms of polyneuropathy and/or dysautonomia (postural hypotension, syncope, erectile dysfunction, gastrointestinal mobility alterations)
• Nephrotic syndrome (edema, albuminuria progressing to renal failure)
• Hepatomegaly (with cholestasis)
• "Resolution" of hypertension
• Exertional dyspnea, fatigue, and peripheral edema
• Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interventricular septum, interatrial septum, and right ventricular free wall
• Reduction in longitudinal strain with apical sparing
• Discrepancy between left ventricular thickness and QRS voltage (with a lack of left ventricular hypertrophy on EKG)
• Atrioventricular block, in the presence of increased, left ventricular wall thickness
• Cardiac Magnetic Resonance features (marked extracellular volume expansion, abnormal nulling time for the myocardium, or diffuse late gadolinium enhancement)

What screening and early detection methods for amyloidosis should be implemented?

The benefits of screening for monoclonal proteins are under evaluation in the Icelandic controlled study iStopMM whose outcome is eagerly awaited [2]. For early detection of AL amyloidosis in patients followed for IgM MGUS or WM, it is recommended to measure annually the 24-hour urinary albumin concentration or the urinary albumin/creatinine ratio [3,4], serum N-terminal pro-brain natriuretic peptide (NT-proBNP), and alkaline phosphatase concentrations in order to detect early renal, cardiac, and liver amyloid involvement [5]. Red flags reported in Table 1 should also raise suspicion of systemic amyloidosis [6]. Furthermore, in some referral centers, it is now possible to identify light chains (LCs) with a high propensity to form amyloid based on algorithms developed using machine learning applied to the LC sequences [7,8]. Patients with highly amyloidogenic LCs should be followed more regularly with biomarkers of amyloid organ involvement to start therapy in the very early stage of the disease.

How should incidental (asymptomatic) amyloidosis be handled?

Patients with amyloid deposits incidentally identified (such as in bone marrow biopsy or other biopsies), but without signs of organ damage, should be followed with serial measurements of urinary albumin, NT-proBNP, and alkaline phosphatase, every 6 months to detect early organ deterioration and for prompt therapy. NT-proBNP <180 ng/L and hs-TnT <14 ng/L reliably exclude the diagnosis of cardiac amyloidosis [9]. If an increase of either biomarker above these thresholds is observed during follow-up, cardiac magnetic resonance can be considered to confirm cardiac involvement. If cardiac magnetic resonance is not available, echocardiography may be considered. Advise to counsel patients to report amyloidosis-related symptoms directly and not wait until the next appointment.

What are the essential tests for amyloidosis work-up?

The essential tests for amyloidosis work-up are reported in Table 2. Particular attention should be devoted to the accurate typing of amyloid deposits, considering that in patients with the age of presentation typical of WM, wild type transthyretin amyloidosis can also occur [10] and that sporadic cases of WM patients with reactive (AA) amyloidosis have been reported [11] Table 3.

How do we manage amyloidosis in IgM-related disorders vs WM patients?

Bone marrow biopsy/aspirate is essential for deciding on the management. If the underlying clone is lymphoplasmacytic, we may use the same armamentarium as in WM, with some notable differences. WM disease control only does not suppress the amyloidogenic light chain enough and the goal of therapy is a very good partial response or complete response (VGPR/CR) response as soon as possible in amyloidosis patients. Therefore, autologous stem cell transplantation (ASCT) should be considered frontline in eligible patients in view of the excellent outcomes reported with VGPR or better in 76% of patients, with acceptable toxicity (treatment-related mortality 5%) [12]. Furthermore, the increased prevalence of neuropathy in these patients limits the use of bortezomib, but rituximab-bendamustine can be applied in patients not receiving frontline ASCT. Ibrutinib has been reported in a small series of patients to produce unsatisfactory control of the light chain and poor tolerability [13,14]. Newer Bruton's tyrosine kinase (BTK) inhibitors, such as zanubrutinib, with higher efficacy and better tolerability, deserve further investigation [15]. If the clone is prevalently plasmacytic, the therapy should follow the guidelines for non-IgM-related AL amyloidosis [16,17]. In the rare cases of marginal zone lymphoma, and other non-lymphoplasmacytic lymphomas, associated with AL amyloidosis, current therapies for these lymphomas should be considered, although the regimen of bendamustine-rituximab is probably very effective in these conditions [18]. Along with clone-directed therapy, patients with WM-related amyloidosis also require additional supportive care, such as blood pressure support in those with orthostasis, symptom management for peripheral neuropathy, and diuresis for edema associated with heart failure or nephrotic syndrome.

How should light chain response be used for treatment response in WM-related amyloidosis?

Since the cause of the disease is the amyloidogenic LC, the same response criteria validated for non-IgM AL amyloidosis should be used while waiting for validation in large patient populations of IgM amyloidosis [19,20]. These response criteria are based solely on the modifications of the LC concentration, and the aim of therapy is a VGPR/CR response as soon as possible, possibly within 2 months [21]. In cases where the involved LC concentration at diagnosis is < 20 mg/L, the hematological response can be based on the modifications of the IgM concentration following the consensus criteria for WM [22], recently updated by consensus panel 4 from

Table 2
Essential tests for workup of the suspected WM patient with amyloidosis.

Target	Tests
Clone	• Bone marrow biopsy and aspirate (immunohistochemistry, flow cytometry, FISH, and Congo red staining) • **Search for *MYD88*, *CXCR4* mutations** • computerized tomography (CT) of chest, abdomen, and pelvis • Serum electrophoresis, serum and urine immunofixation, quantitative test for LC, IgG, IgA, IgM and Bence Jones proteinuria.
Tissue diagnosis & typing	• Biopsy sites: abdominal fat →(salivary glands) →involved organ • **Typing**[§]: MS or immunoelectron microscopy, DNA analysis (DNA analysis if clinically indicated)
Heart	• Biomarkers (NT-proBNP or BNP if renal failure, cardiac troponins) • Echocardiography (with strain imaging), cardiac MRI • electrocardiogram (+Holter ECG) • **Scintigraphy with DPD/PYP**[*]
Kidney	• 24 h albuminuria, s. creatinine and eGFR
Liver	• Liver function tests (alkaline phosphatase, alanine transaminase bilirubin) • Liver imaging (echo, CT) if abnormal function tests

LC = light chains.
[*] The indication to perform scintigraphy with DPD/PYP in elderly patients (>60 y) with cardiac involvement is still under debate. In patients achieving CR but without cardiac response, scintigraphy may help in clarifying the reason for the lack of improvement in cardiac function. If DPD/PYP scintigraphy is negative, the investigation of MRD can show the persistence of the clone and the need for further anticlone therapy.
[§] Typing is necessary to treat the proper cause of amyloidosis.

Table 3
Summary of CP6 recommendations.

Early diagnosis	In patients followed for IgM MGUS or WM, measure annually the 24-h urinary albumin concentration, or the urine albumin/creatinine ratio, serum NT-proBNP, and alkaline phosphatase concentrations to detect early renal, cardiac, and liver amyloid involvement Look for red flags in medical history and additional investigations (see Table 1) Patients with amyloid deposits incidentally identified (such as in bone marrow biopsy or other biopsies), but without signs of organ damage, should be followed every 6 mo with serial measurements of urinary albumin, NT-proBNP, and alkaline phosphatase
Diagnosis	Typing is necessary to treat the proper cause of amyloidosis, this can be done with mass spectrometry-based methods, immuno-electron-microscopy, and immunohistochemistry
Treatment	The goal of therapy is a VGPR/CR response as soon as possible ASCT should be considered frontline or as consolidation in view of the excellent outcomes Rituximab-bendamustine can be applied in nontransplant eligible patients as a first-line therapy
Response	Since the cause of the disease is the amyloidogenic LC, the same response criteria validated for non-IgM AL amyloidosis should be used. In the rare cases of AH amyloidosis or low light chain levels at diagnosis, the WM response criteria (following IgM levels) should be utilized. Lymph node involvement should not be considered for the assessment of hematological response since these may contain amyloid

the 11th International Workshop on Waldenström's macroglobulinemia on diagnostic and response criteria reported in this issue. In non-IgM AL amyloidosis, the clinical relevance of searching for trace amount of LC in patients in CR using conventional criteria is being explored [23] as well as the achievement of minimal residual disease negativity [24,25]. These studies indicate that the elimination of the residual disease is associated with improved cardiac response and extended survival. Although in AL amyloidosis associated with WM these data are lacking, the same principle likely applies.

Will adenopathy resolve in patients with WM-associated AL amyloidosis?

In WM, lymph node enlargement is caused by lymphoplasmacytic infiltration, and therefore it is one criterion for response [22]. In contrast, in IgM-related amyloidosis, lymph node enlargement is usually caused by amyloid deposition [26], and reabsorption of the amyloid deposits may require several months-years after achieving a hematological response or does not occur at all. For this reason, changes in lymph node size should not be considered for the assessment of hematological response in IgM-related amyloidosis.

What ASCT ablative regimens should be used in WM-related amyloidosis?

There are no comparative studies for induction with high-dose melphalan vs BEAM regimen (Carmustine, Etoposide, Cytarabine, and Melphalan). The outcome of conditioning with BEAM is reported by the Mayo Clinic investigators. All 6 patients receiving BEAM conditioning achieved a VGPR, while 32 patients treated with high-dose melphalan achieved VGPR or CR in 72% of cases [12]. However, considering the lower toxicity of MEL200 and the high response rate achieved, it is probably to be the preferred myeloablative regimen in WM-related amyloidosis.

Why is it important to obtain amyloid typing?

The diagnostic process of systemic amyloidosis is rather complex as illustrated in Fig. The possible occurrence of transthyretin cardiac amyloidosis in elderly patients requires an accurate diagnostic approach that should initiate with the search for the monoclonal protein with appropriate methodology [21]. As reported above, amyloid typing is essential to assure proper therapy and should be performed in every patient. In fact, in this age range, the occurrence of wild-type transthyretin cardiac amyloidosis, particularly in males, should always be considered. In addition, in rare cases, WM was associated with AA amyloidosis, probably due to high levels of IL-6 observed in patients with WM [11]. Typing of amyloid deposits should be preferentially performed using mass spectrometry-based methods, although immuno-electron-microscopy and immunohistochemistry using highly specific antibodies are also acceptable at experienced centers [5]. If not readily available, most of these methods are likely available at a collaborating institution.

How do we manage WM patients with TTR-related amyloidosis?

The therapy of TTR amyloidosis targets specific steps of the amyloid cascade, from suppressing the production of the amyloid protein precursor through TTR gene silencing or knockout to the kinetic stabilization of the TTR tetramer [27]. A kinetic stabilizer,

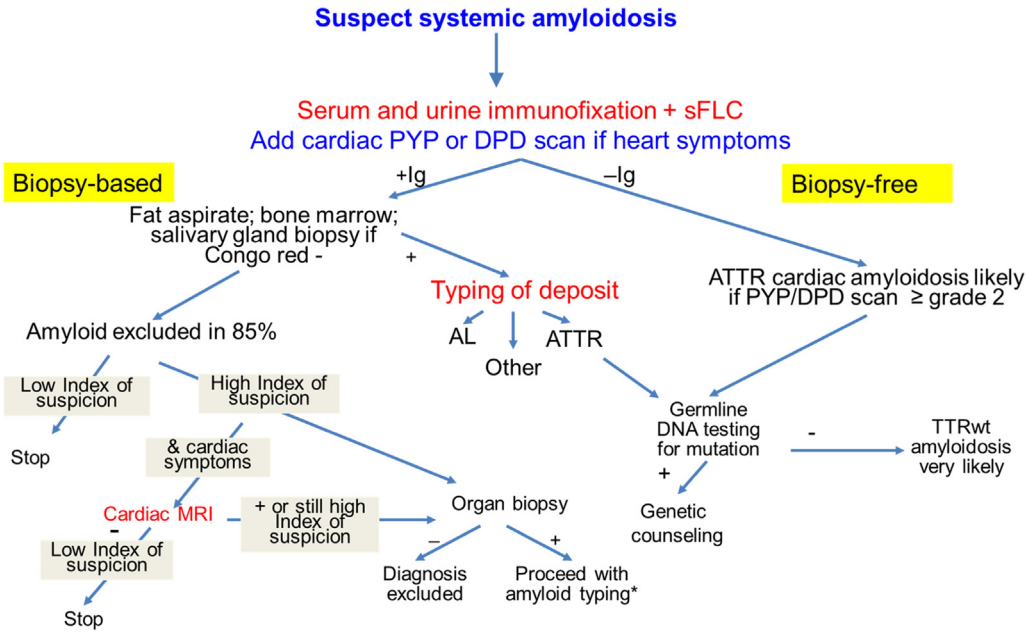

Fig. Algorithm for Systemic Amyloidosis Workup. The big divide of the diagnostic flowchart is the presence of a monoclonal protein (+Ig) that imposes the tissue biopsy followed by amyloid typing preferentially performed by mass spectrometry-based methods. In absence of a monoclonal protein (-Ig) the strong uptake (≥ grade 2 of the Perugini score) [31] of labeled bone tracers DPD or PYP, is sufficient to diagnose transthyretin cardiac amyloidosis [32]. The subsequent genetic analysis will further differentiate between wild-type and hereditary transthyretin amyloidosis.

tafamidis, has been approved for cardiac ATTR amyloidosis, while the other agents are expected to enter the treatment of cardiac amyloidosis in the near future. Based on their mechanism of action, none of these drugs are expected to interfere with anticlone therapy for WM. Therefore, in the presence of these 2 diseases, ATTR amyloidosis and WM, we can treat properly each condition with no significant drug interference. However, ATTR amyloidosis is a severely debilitating condition exposing patients to reduced tolerability of anticlone therapy. Patients with cardiac ATTR amyloidosis and associated WM are more fragile and this may affect the possibility to treat WM with aggressive therapies, such as ASCT, and, in general, expose the patients to more severe adverse events (eg, cardiac toxicity in those receiving BTK inhibitors). Similarly, in patients with ATTR amyloidosis and autonomic neuropathies, the presence of postural hypotension limits the use of proteasome inhibitors. Supportive therapies should be instituted to improve cardiac function, control neuropathic pain, augment orthostatic hypotension, and, very importantly, provide nutritional support to counteract cachexia in ATTR amyloidosis.

Concluding remarks

The diagnosis and management of AL amyloidosis are articulated and complex due to the molecular mechanisms underlying the disease and the multisystem involvement that renders the diagnosis difficult and requires a risk-adapted therapeutic approach. When the clone producing the amyloidogenic LC is predominantly lymphoplasmacytic with the production of a monoclonal IgM, usually the patients present with lower concentrations of serum LC, less severe cardiac involvement, more frequent neuropathies, and more lung and soft tissues involvement [26,28]. The hematologist should keep a high level of alert to detect the clinical red flags and follow patients with IgM monoclonal gammopathy with serial measurements of sensitive biomarkers of amyloid organ involvement. The aim of therapy is a very rapid and profound reduction of the concentration of the amyloid protein, a goal that is difficult to achieve in an indolent, but difficult to eradicate disease, such as WM. In this context, high-dose melphalan, or possibly BEAM, preferentially within a trial, seems to be the most effective approach in terms of rapidity and depth of response in eligible patients. The assessment of the response may be problematic due to the frequently low concentrations of LC (one-fifth of the patients) and the new mass spectrometry-based technology may help in defining the quality of the response. While in WM the goal is to keep the clone under control for a long time, without necessarily eradicating it based on a careful risk/benefit balance in frequently elderly and frail patients, in the presence of the very toxic LC found in WM-related AL amyloidosis eradication is indeed the goal. Very effective and better tolerated therapies are now emerging for WM [29,30] and there is hope that clone annihilation can be achieved in the near future in AL amyloidosis associated with WM.

Author contributions

GM, MCM, SRS, RGS, JSM, and MD prepared, reviewed and submitted key questions for Consensus Panel 6 (CP6). Questions were reviewed in an open general assembly by attendants of IWWM-11, and additional questions for CP6 deliberations were formulated and submitted. GM wrote the first draft of CP6 responses, and draft was reviewed and modified by MCM, SRS, SPT, RGS, JSM, and MD. Final draft was submitted to CP6 general panel for review and commentary. CP6 general panel was composed of individuals with experience in the care of WM patients who attended IWWM-11 and volunteered to be on CP6 panel (GB, XC, MG, CFL). All Authors read and approved the submitted manuscript.

Declaration of Competing Interest

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