What is the optimal work-up and treatment approach for the WM patient with amyloidosis?

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In AL amyloidosis, a monoclonal light chain (LC) misfolds, aggregates, and deposits in tissues, causing organ dysfunction and ultimately death if left untreated. An IgM clone is responsible for the disease in approximately 4% to 7% of cases. Immunoglobulin M (IgM)-related amyloidosis remains a rare and little-known complication of monoclonal IgM-associated disorders, and it may be easily missed. Older patients with IgM-AL amyloidosis are being increasingly recognized posing particular challenges in management.Early diagnosis is essential and can be achieved using biomarkers of cardiac (NT-proBNP) and renal (proteinuria) dysfunction.Characterization of the amyloid deposits is a central step in the diagnostic process, since AA amyloidosis reactive to chronic inflammation can be also associated with Waldenström macroglobulinemia, though in only 4% of cases, and the possibility of concomitant hereditary or senile amyloidosis cannot be ignored in this elderly population. If necessary, referring patients to a specialized center should be considered. Accurate characterization of the underlying clonal disorder, that must include specific gene studies (MYD88) is critical in the diagnostic work-up of patients with IgM-AL amyloidosis. Recent reports indicate that *MYD88 L265P* positive patients had a lower rate of cardiac involvement and a higher incidence of amyloid neuropathy.Treatment should be tailored according to the underlying IgM-related condition and should aim at reducing the concentration of the LC rapidly and deeply (aiming at VGPR or better), since it has been shown that the quality of the hematological response to treatment affects survival. Considering the absolute need of a rapid elimination of the amyloid precursor, rapidly acting regimens should be preferred. Currently, bortezomib-based regimens and ASCT seem to be associated with the best responses. It is essential to accurately target the lymphoid component of the clone for longer term disease control. The promising results of the first studies on new therapies targeting the amyloid deposits indicate that in future combination therapies will be used.