Diagnostic Workup and management of WM-related Amyloidosis

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Waldenström Macroglobulinemia (WM) is associated with AL amyloidosis in approximately 7.5% of patients. These cases show unique features, including a higher prevalence of kappa light chains (LC) compared to typical AL amyloidosis. The kidneys, heart, nerves, lungs, and lymph nodes are the most commonly affected organs in these patients. Due to the potential for significant organ dysfunction, the monitoring, diagnostic approach, and management of these patients differ from those with only WM or with non-IgM-related AL amyloidosis.

Early diagnosis is critical and can be facilitated by using sensitive biomarkers to detect amyloid organ involvement during follow-up of WM-related MGUS. Key biomarkers include NT-proBNP for heart involvement, proteinuria for kidney involvement, and alkaline phosphatase for liver involvement.

A thorough diagnostic workup is required and should include a bone marrow biopsy to characterize the infiltrate, which may show lymphoplasmacytic lymphoma or a pure plasma cell population. This distinction is crucial for treatment planning. Genetic testing for *MYD88* and *CXCR4* variants, as well as FISH analysis, should be performed. The presence of amyloid deposits must be confirmed by biopsy, followed by typing, preferably using mass spectrometry.

The evaluation of treatment response should follow the modified criteria for WM and those used for AL amyloidosis. In rare cases, such as AH amyloidosis or low light chain levels at diagnosis, WM response criteria based on IgM levels should be used. The primary treatment goal is to eliminate the amyloid-producing light chains. WM-associated AL amyloidosis is rare, and there are no large, high-quality trials to guide treatment decisions. Current recommendations are based on case series, retrospective

reviews, and expert opinions from academic centers. If the underlying clone is lymphoplasmacytic, treatment options similar to those used in WM may be applied, with some differences. Autologous stem cell transplantation (ASCT) should be considered as frontline or consolidation therapy due to its favorable outcomes.

For non-transplant-eligible patients, Rituximab-bendamustine is a recommended first-line therapy, while zanubrutinib is preferred over older BTK inhibitors due to better tolerability. In patients with a pure plasma cell infiltrate in the bone marrow, treatment should follow AL amyloidosis guidelines, with venetoclax being a consideration for those with the t(11;14) translocation. Supportive care is essential to manage symptoms while disease-modifying therapy takes effect.

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