

Impact of Chemoimmunotherapy for Primary Cold Agglutinin Disease and Waldenström Macroglobulinemia-associated Cold Agglutinin Syndrome

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Background: Cold agglutinins (CA) are autoantibodies, typically IgM- κ , that bind red blood cell antigens at low temperatures and trigger complement-mediated hemolysis. Cold agglutinin-associated hemolysis (CAH) occurs in diverse clinical contexts, including primary cold agglutinin disease (pCAD) and Waldenström macroglobulinemia-associated cold agglutinin syndrome (WM-CAS). The differentiation of these entities is often challenging, particularly in MYD88 L265P-negative cases. pCAD is generally managed with complement-directed therapy or neoplastic cell clone-directed therapy, including chemoimmunotherapy (CIT), on the other hand, WM-CAS is treated as symptomatic WM. However, many studies that evaluated CIT for CAH lacked accurate diagnostic examination to distinguish between pCAD and WM-CAS. Consequently, it remains unclear whether the disease classification affects the clinical presentation, responses to CIT, and outcomes of patients with CAH. Therefore, we retrospectively analyzed patients with CAH (pCAD and WM-CAS) and WM without CAS (WM-only) to compare clinicopathological features, responses to CIT, long-term outcomes, and adverse events (AE), including thrombotic events.

Methods: We retrospectively analyzed patients with pCAD, WM-CAS, and WM without CAS (WM-only) treated at the National Hospital Organization Disaster Medical Center between Apr 2010 and Nov 2025. Diagnoses followed the revised fifth edition of the WHO Classification of Haematolymphoid Tumours. Cases of CAS secondary to infections or malignant disorders other than WM were excluded. These exclusions were based on a comprehensive evaluation including clinical presentation, laboratory findings, a pathological assessment, and MYD88L265P analysis. Clinicopathological features and outcomes were compared. Treatment responses were assessed using CAD-specific criteria based on hemoglobin and hemolysis markers. Time to next treatment (TTNT) and overall survival (OS) were analyzed using Kaplan-Meier methods. This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at our hospital (Disaster Medical Center IRB 2025-42).

Results: Ten patients had CAH (5 pCAD, 5 WM-CAS) and 29 had WM-only. CAH cases showed higher lactate dehydrogenase and total bilirubin levels, whereas WM-only cases had higher serum IgM levels and greater bone marrow involvement. Rituximab-based CIT predominated as the first-line therapy for both pCAD and WM-CAS. Overall response rates were 100% in pCAD and 80% in WM-CAS, with similar kinetics. With the median follow-up duration was 81 months, TTNT did not significantly differ between pCAD and WM-CAS. Median TTNT was not reached in the CAH group, while that was 65 months in the WM-only group ($p = 0.0417$). Elevated FDP was more frequent in CAH cases, while no overt thrombotic events or grade ≥ 3 infections were observed.

Conclusions: Rituximab-based CIT effectively controlled CAH in both pCAD and WM-CAS, with similar durability. When hemolysis is the dominant clinical issue and the disease classification is unclear, tumor-directed therapy might be one of the reasonable treatment options.

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