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

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Article

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

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Simple Summary

Cold agglutinin-associated hemolysis (CAH) is a condition in which red blood cells are destroyed by abnormal antibodies, leading to anemia and related symptoms, including overt thrombotic events. CAH may occur as cold agglutinin disease (pCAD) or cold agglutinin syndrome in association with Waldenström macroglobulinemia (WM-CAS). In clinical practice, distinguishing between these diseases is often difficult, particularly when advanced genetic testing is unavailable. Furthermore, it remains unclear whether a precise diagnosis significantly affects treatment outcomes. In this retrospective study, we compared the clinical features, treatment responses, and long-term outcomes of patients with pCAD, WM-CAS, and WM without hemolysis treated with chemoimmunotherapy (CIT). CIT effectively attenuated CAH in the pCAS and WM-CAS groups with similar response durability and long-term outcomes. These results suggest the potential of tumor-directed CIT as a practical and effective treatment approach, even without a precise disease classification.

Abstract

Background: 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. Since studies that examined the effects of chemoimmunotherapy (CIT) frequently predated routine molecular testing, it remains unclear whether the disease classification has an impact on treatment responses and durability. **Methods:** We retrospectively analyzed patients with pCAD, WM-CAS, and WM without CAS (WM-only) treated at a single center between April 2010 and November 2025. Diagnoses followed the revised fifth edition of the WHO Classification of Haematolymphoid Tumours. 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. **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. TTNT did not significantly differ between pCAD and WM-CAS. Elevated FDP was more frequent in CAH, while

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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 represents a treatment strategy.

Keywords: cold agglutinin disease; cold agglutinin syndrome; waldenström macroglobulinemia; chemoimmunotherapy

Introduction

Cold agglutinins (CA) are autoantibodies (typically immunoglobulin (Ig) M-κ) that bind red blood cell antigens at low temperatures and trigger complement-mediated hemolysis (1). CA-associated hemolysis (CAH) occurs across diverse clinical contexts, including lymphoid malignancies, infections, and autoimmune diseases (2-6). In addition, CAH may increase the incidence of thrombotic events as well as mortality (7-9).

In the fifth edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours, primary CA disease (pCAD) is defined as a neoplastic CA-producing condition arising from clonal B-cell proliferation that does not meet the diagnostic criteria for a specific B-cell lymphoma (10), whereas CAH associated with other underlying disorders, including B-cell lymphomas, is classified as CA syndrome (CAS) (11). However, difficulties are associated with differentiating between pCAD and Waldenström macroglobulinemia-associated CAS (WM-CAS) in routine practice. Although *MYD88 L265P* mutation (*MYD88*^{L265P}) testing and *IGHV4-34* usage are considered informative because *MYD88*^{L265P} is detected in approximately 90% of WM cases (12), while IGHV4-34 usage is reported in the vast majority of CAD cases (13, 14), these molecular assessments are not always available, and diagnoses often rely on an integrated clinical and pathological evaluation (14). In clinical practice, strict categorization may not be always feasible.

Despite these diagnostic challenges, therapies targeting the underlying clonal disorder are widely used in clinical practice for patients with CAH. In WM-CAS, CAH is regarded as a symptomatic manifestation of WM (15) and is managed according to WM treatment recommendations (16); in contrast, pCAD may be managed with B-cell or plasma cell clone-directed therapy, including rituximab-based regimens (17-22), Bruton tyrosine kinase inhibitors (23), and anti-CD38 monoclonal antibodies, such as daratumumab (24), and/or complement-directed therapy, including sutimlimab (25).

However, many studies that evaluated chemoimmunotherapy (CIT) for CAD missed routine molecular testing and, thus, were unable to reliably distinguish pCAD from 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

Patients and Study Design

We conducted a retrospective review of consecutive patients diagnosed with pCAD and WM (with or without CAS) who were treated at the National Hospital Organization Disaster Medical Center between April 2010 and November 2025. The diagnoses of pCAD and WM were established in accordance with the revised fifth edition of the WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (10, 26).

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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 *MYD88*^{L265P} analysis.

Data Collection

Clinical information was obtained from electronic medical records and included demographic characteristics (age and sex) and the performance status (27). Hematological and biochemical parameters included the levels of hemoglobin, total bilirubin, lactate dehydrogenase (LDH), serum IgM, and fibrin degradation products (FDP). Additional clinical variables included CA titers; the presence of splenomegaly, lymphadenopathy, hyperviscosity syndrome, and B symptoms; and transfusion requirements. Bone marrow (BM)-based variables included cytogenetic abnormalities, the mutational status of *MYD88*^{L265P} and *CXCR4*^{WHIM}, and the percentages of lymphocytes and plasma cells in BM specimens. Treatment-related variables included treatment regimens, treatment responses, times to responses, treatment-related AE graded according to the Common Terminology Criteria for Adverse Events (28), time to next treatment (TTNT), and overall survival (OS). TTNT was defined as the time from the initiation of first-line systemic therapy to the initiation of the next systemic therapy or death, whichever occurred first; in pCAD, next-line therapy was triggered by the need for additional treatment for recurrent or persistent hemolysis, in WM-only by the International Workshop on Waldenström's Macroglobulinemia (IWWM) response criteria (29), and in WM-CAS by hemolysis and/or the IWWM response criteria. OS was defined as the time from the initiation of first-line systemic therapy to death. The data cut-off date was 30 November 2025.

Pathological and Genetic Analyses

BM aspirates and biopsy specimens were reviewed to classify CAH cases as pCAD or WM-CAS, in accordance with the revised fifth edition of the WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (10, 26).

All cases harboring *MYD88*^{L265P} were classified as WM in this clinical context (26). In *MYD88*^{L265P}-negative cases presenting with CAH, the disease classification was primarily based on BM biopsy findings, with BM aspiration findings being used as supportive information.

Cases were classified as pCAD when BM biopsy showed intraparenchymal nodular infiltrates without overt tumor infiltration, composed predominantly of small lymphoid cells with limited diffuse plasma cell involvement. In contrast, cases were classified as WM when BM biopsy revealed various infiltration patterns, including diffuse involvement, with admixed populations of small B cells, lymphoplasmacytic cells, and plasma cells, consistent with previously reported pathological features (14). BM aspiration findings showing overt tumor cell infiltration were considered to be supportive of a diagnosis of WM.

A conventional chromosome banding analysis was performed on BM aspirates obtained at the time of the initial diagnosis. Genetic analyses were conducted using droplet digital PCR (ddPCR) with the QX200 AutoDG Droplet Digital PCR System (Bio-Rad). Commercial ddPCR mutation detection assays (Bio-Rad) were used to identify *MYD88*^{L265P} and *CXCR4* mutations, including *T318* frameshift, *S338* nonsense, and *S338* frameshift variants, as previously described-(30).

Treatment and Response Assessment

Initial treatment regimens were selected at the discretion of the treating physicians according to contemporaneous clinical practice.

Treatment responses in patients with CAH (pCAD and WM-CAS) were assessed using CAH response criteria, as applied in previous clinical studies on ibrutinib and daratumumab (23, 24). In WM-CAS, tumor responses were also assessed using IWWM response criteria (29); WM-only responses were assessed using the IWWM criteria. According to CAH response criteria (23, 24), a CAH-complete response (CAH-CR) was defined as a hemoglobin level >12 g/dL, resolution of the

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clinical signs of hemolysis, independence from red blood cell transfusion, and the normalization of total bilirubin and LDH levels. A CAH-partial response (CAH-PR) was defined as a hemoglobin level of 10-12 g/dL or an increase of ≥2 g/dL from baseline without recent transfusion, accompanied by improvements in hemolytic markers without complete normalization. Patients who did not meet these criteria were classified as having no response. The overall response rate (ORR) was calculated as the percentage of patients achieving CAH-CR or CAH-PR.

Statistical Analysis

TTNT and OS were analyzed using the Kaplan-Meier method, and differences between groups were assessed using the Log-rank test. Comparisons of categorical variables between two groups were performed using Fisher's exact test, and comparisons of continuous variables were conducted using the Wilcoxon rank-sum test. In Figure 1, 95% confidence intervals around the median trajectories were estimated using bootstrap resampling. All statistical analyses were performed using Stata version 18 (StataCorp [LLC], College Station, TX, USA).

Results

Patient Characteristics

Five patients had pCAD, five had WM-CAS, and 29 had WM-only. Baseline characteristics are summarized in Table 1. Characteristics stratified by the presence or absence of CAH are shown in Supplementary Table S1.

Median serum IgM levels were 232 mg/dL in pCAD, 697 mg/dL in WM-CAS, and 3,191 mg/dL in WM-only. FDP elevation was more frequent in pCAD and WM-CAS than in WM-only, being observed in 3/5 patients (60%), 2/5 patients (40%), and 3/29 patients (10%), respectively. In contrast, MYD88 L265P was detected predominantly in WM-only, being absent in pCAD, present in 1/4 WM-CAS patients (25%), and detected in 27/29 WM-only patients (93%).

Table 1: Patient characteristics according to disease phenotype (primary CAD, WM-CAS, and WM without CAS)

Characteristic	(1) primary CAD (N = 5)	(2) WM with CAS (N = 5)	(3) WM without CAS (N = 29)
Median age, years (range)	68 (48-85)	71 (64-80)	71.5 (49-85)
Sex (M/F), n	2/3	2/3	25/4
PS > 1, n (%)	3/5 (60)	2/5 (40)	7/29 (24)
Hb < 11.5 g/dL, n (%)	5/5 (100)	4/5 (80)	22/29 (76)
Plt < 100 × 10^9 /L, n (%)	0/5	1/5 (20)	2/29 (7)
β2MG > 3 mg/L, n (%)	0/3	3/5 (60)	18/27 (67)
Serum ALB < 3.5 g/dL, n (%)	1/5 (20)	1/5 (20)	19/29 (66)
LDH > 250 IU/L, n (%)	3/5 (60)	1/5 (20)	1/28 (4)
FDP > ULN μg/mL, n (%)	3/5 (60)	2/5 (40)	3/29 (10)
Median serum IgM, mg/dL (range)	232 (162-1077)	697 (327-6810)	3191 (341-7682)
Median M-protein, g/dL (range)	1 (0.8-1.3)	1.4 (0.8-3.9)	3 (1.1-6.6)
MYD88 L265P mutation, n (%)	0/4	1/4 (25)	27/29 (93)
CXCR4 mutation, n (%)	0/4	0/4	3/29 (10)
Deletion chromosome 17p, n (%)	0/5	0/4	2/25 (8)
Complex karyotype, n (%)	0/5	1/4 (25)	4/29 (14)
Hyperviscosity, n (%)	0/5	0/5	12/29 (41)
B-symptom, n (%)	0/5	0/5	8/29 (28)
Splenomegaly, n (%)	4/5 (80)	2/5 (40)	7/29 (24)
Lymphadenopathy, n (%)	0/5	1/5 (20)	11/29 (38)
Median total neoplastic cells in BM, % (range)	19 (8-33)	30.7 (18.8-62)	47.1 (35.1-86.7)

Abbreviations: CAD, cold agglutinin disease; WM, Waldenström macroglobulinemia; CAS, cold agglutinin syndrome; PS, performance status; Hb, hemoglobin; Plt, platelets; β2MG, β2-microglobulin; ALB, albumin; LDH, lactate dehydrogenase; FDP, fibrin/fibrinogen degradation products; IgM, immunoglobulin M; BM, bone marrow.

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Individual Characteristics of CAH

The individual characteristics of the 10 CAH cases are shown in Table 2. The underlying diagnoses were pCAD in 5, which had been previously classified as symptomatic pCAD (19), and WM-CAS in 5 patients.

In the pCAD group, the *MYD88*^{L265P} analysis was performed on four patients and none had the mutation. Regarding marrow infiltration patterns, three patients (Case 1, 2, 5) showed a nodular pattern, whereas no overt neoplastic infiltration was identified in the remaining cases.

In the WM-CAS group, the *MYD88*^{L265P} analysis was available for four patients and was positive in 1/4 (Case 6). Case 10 had lymphadenopathy. Cases 7 and 9 showed diffuse BM infiltration on biopsy. Case 8 showed a nodular pattern on biopsy; however, 31% of tumor cell infiltration was confirmed in a BM aspirate, and the case was diagnosed as LPL.

Table 2. Individual patient characteristics with cold agglutinin-associated hemolysis

Case	Underlying disease	Age/Sex	Hb (g/dL)	T-bil (mg/dL)	IgM (mg/dL)	CA Titer	Splenomegaly	Lymph-adenopathy	Isotype of the M protein	G-banding	MYD88 mutation	CXCR4 mutation	Bone marrow involvement pattern	Lymphocytes and plasmacytes in BM	RBC transfusion before therapy (U/month)
1	pCAD	61/M	9	3	1077	4096	+	-	IgM-κ	normal karyotype	wild type	wild type	nodular	20%	8
2	pCAD	68/M	7.5	2.8	191	256	+	-	IgM-κ	47, XY, +X [20/20]	wild type	wild type	nodular	18%	4
3	pCAD	48/F	3.9	2.2	888	512	+	-	IgM-κ IgG-κ	normal karyotype	wild type	wild type	No aggregates	4.4%	6
4	pCAD	74/F	7.9	2.8	232	2048	-	-	IgM-κ	normal karyotype	wild type	wild type	No aggregates	10.4%	4
5	pCAD	85/F	7.9	1.2	162	512	+	-	IgM-κ	normal karyotype	NA	NA	nodular	11%	0
6	WM	80/M	9.3	0.8	1340	64	-	-	IgM-κ	normal karyotype	Mutated	wild type	nodular	36%	0
7	WM	76/F	5.3	1.8	6810	2048	+	-	IgM-κ IgA-λ	49,XX, +add(1)(p11), +18, +20 [2/20]	wild type	wild type	diffuse	62%	8
8	WM	64/M	11.9	3.7	327	1024	+	-	IgM-κ IgG-κ	normal karyotype	wild type	wild type	nodular	31%	0
9	WM	68/F	9	0.6	627	256	-	-	IgM-κ	normal karyotype	wild type	wild type	diffuse	28%	0
10	WM	71/M	6.8	6.1	697	4096	-	+	IgM	NA	NA	NA	nodular	19%	8
Median (range)		69.5 (48–85)	7.9 (3.9–11.9)	2.5 (0.6–6.1)	662 (162–6810)	768 (64-4096)								19.5% (4.4–62)	4 (0-8)

Abbreviations: pCAD, primary cold agglutinin disease; WM, Waldenström macroglobulinemia; M, male; F, female; Hb, hemoglobin; T-bil, total bilirubin; IgM, immunoglobulin M; CA, cold agglutinin; BM, bone marrow; RBC, red blood cell; U, units; LPL NA, not applicable.

Treatment Regimens

Treatment regimens were distributed as follows. In the pCAD group, four patients received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), and one received bendamustine plus rituximab (BR) (22). In the WM-CAS group, R-CHOP was administered to five patients (31). In the WM-only group, R-CHOP was the most frequently used regimen (n=20), followed by BTK inhibitors (n=5), BR (n=1), rituximab monotherapy (n=1), bortezomib-based regimens (n=1), and other treatments (n=1).

Response of Hemolytic Anemia Assessed by CAH Response Criteria

Figure 1a shows chronological changes in hemoglobin and total bilirubin levels, reflecting the treatment responses of hemolytic anemia in patients with-pCAD and WM-CAS.

In the pCAD group, all patients (5/5) achieved at least CAH-PR (ORR 100%). The median time to CAH-PR was 3 weeks (range, 1-24). In addition, 4/5 patients achieved CAH-CR, with a median time to CAH-CR of 21.5 weeks (range, 4-41).

In the WM-CAS group, 4/5 patients achieved at least CAH-PR, yielding an ORR of 80%. The median time to CAH-PR was 5 weeks (range, 2-6). In addition, 2/5 patients subsequently achieved CAH-CR, with a median time to CAH-CR of 29.5 weeks (range, 21-38).

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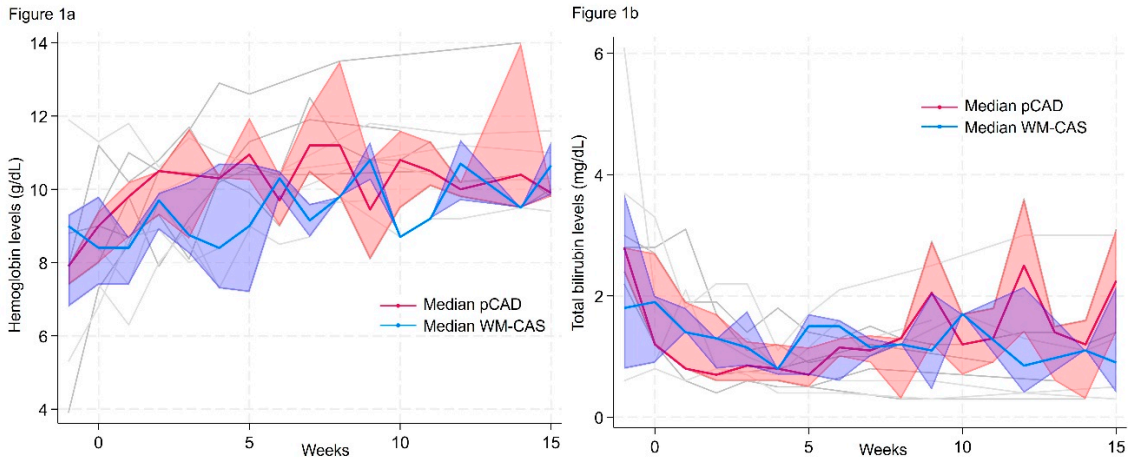

Figure 1. Chronological changes in laboratory findings after treatment. (a) Hemoglobin and (b) total bilirubin over time. The x-axis indicates weeks, with week 0 marking treatment initiation and negative weeks indicating pretreatment measurements. Red and blue lines show median values for primary cold agglutinin disease (pCAD) and Waldenström macroglobulinemia-associated cold agglutinin syndrome (WM-CAS), respectively, with the shaded areas indicating the 95% confidence intervals. Light- and dark-gray lines represent individual patient trajectories for pCAD and WM-CAS.

Tumor Response Assessed by IWWM Response Criteria

Based on IWWM response criteria (29), the best overall responses were CR (n=2), PR (n=2), and SD (n=1) in the WM-CAS group, and CR (n=4), VGPR (n=8), PR (n=10), and SD (n=7) in the WM-only group.

Survival Outcomes

Comparisons of TTNT and OS in patients with CAH (pCAD and WM-CAS) versus WM-only are shown in Figure 2a and Figure 2b, respectively. The median follow-up was 81 months. Median TTNT was not reached in the CAH group and was 65 months in the WM-only group, with a significant difference between the groups (Log-rank p = 0.0417).

TTNT is shown in Figure 3a and OS in Figure 3b for pCAD, WM-CAS, and WM-only. Median TTNT was not reached in the pCAD group, was 39 months in the WM-CAS group, and was 65 months in the WM-only group. TTNT did not significantly differ between pCAD and WM-CAS (Log-rank p = 0.1343).

No deaths occurred in the pCAD group. In the WM-CAS group, one patient died by suicide. In the WM-only group, three patients died of disease progression and one of complications during the follow-up. Median OS was not reached in any group.

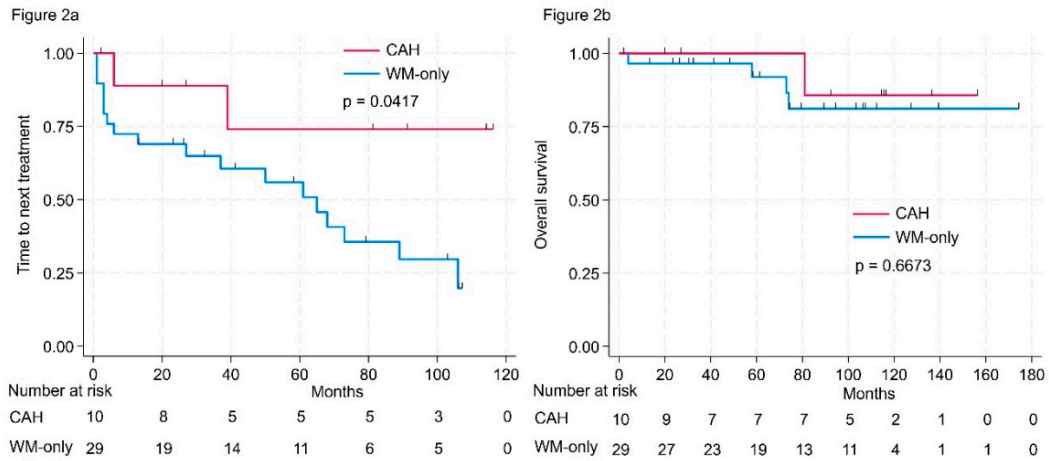

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Figure 2. Survival analyses. (a) Time to next treatment (TTNT) and (b) overall survival (OS). The x-axis shows time in months. Kaplan–Meier curves compare patients with cold agglutinin–associated hemolysis (CAH; primary cold agglutinin disease and Waldenström macroglobulinemia–associated cold agglutinin syndrome) (red) versus patients with Waldenström macroglobulinemia without cold agglutinin syndrome (WM-only) (blue).

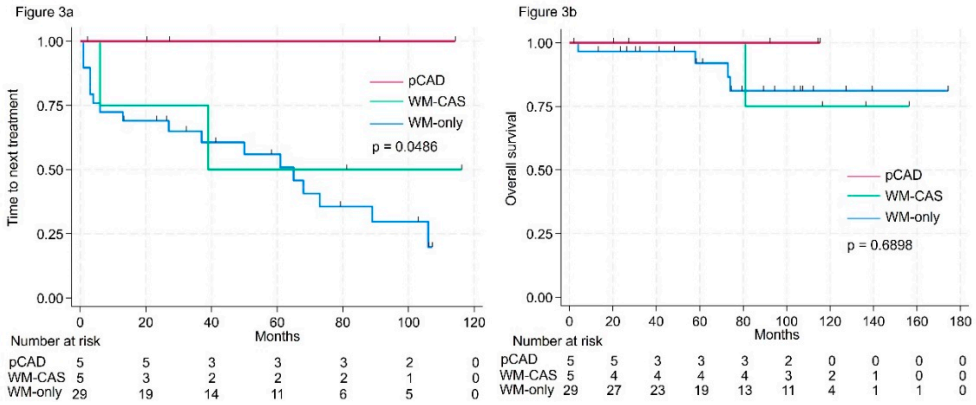

Figure 3. Survival analyses. (a) Time to next treatment and (b) overall survival. The x-axis indicates months. Red, green, and blue curves represent primary cold agglutinin disease (pCAD), Waldenström macroglobulinemia-associated cold agglutinin syndrome (WM-CAS), and Waldenström macroglobulinemia without cold agglutinin syndrome (WM-only), respectively.

AE

Grade 3-4 neutropenia occurred in four pCAD patients and two WM-CAS patients. Two pCAD patients developed grade 2 infections. No thrombotic events occurred among the 10 CAH cases during the follow-up.

Discussion

The accurate differentiation of pCAD from WM-CAS remains challenging in routine clinical practice; however, previous studies indicated the potential of the *MYD88*^{L265P} status, Ig gene usage (e.g., IGHV4-34), and BM infiltration patterns to support the disease classification (14). Somatic hypermutation of the Ig genes is observed in all cases of CAD (13), and *MYD88*^{L265P} is typically absent in CAD (14). In the present study, Ig gene repertoire analysis could not be performed because the analysis was not easily examined in Japan. Similarly, many previous reports did not routinely include IGHV analysis (17-22). In contrast, *MYD88*^{L265P} was negative in all pCAD cases tested (0/4) and was only detected in one of the WM-CAS cases (1/4). Importantly, *MYD88* wild-type (*MYD88*^{WT}) cases have been reported even among WM-CAS; in a multicenter retrospective series on cold autoimmune hemolytic anemia, 2 of 5 WM-associated cases were *MYD88*^{WT} (23). At the same time, available evidence remains insufficient to define the true frequency of *MYD88*^{L265P} positivity or IGHV4-34 usage specifically in WM-CAS, and the BM pathology may be non-discriminatory when the tumor burden is low; therefore, a misclassification, particularly among *MYD88*^{WT} cases, cannot be fully excluded (32, 33). Due to these diagnostic limitations, an important practical question is whether pCAD and WM-CAS show marked differences in treatment responses and durability.

Although pCAD and WM-CAS represent distinct disease concepts and therapeutic paradigms differ in principle, treatment selection in routine clinical practice often overlaps. This may reflect clinically significant hemolysis being a shared driver for interventions in both pCAD and WM-CAS. In WM-CAS, CAH is a symptomatic manifestation of WM (16) and typically prompts WM-directed systemic therapy according to established algorithms (15). On the other hand, in pCAD, treatment options include complement inhibition and clone-directed therapy. Complement inhibition may rapidly control hemolysis, but generally requires ongoing, costly treatment (22, 25, 34) and does not

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target the underlying B-cell clone;. Before the advent of complement inhibition, treatment was therefore largely based on clone-directed approaches, including rituximab monotherapy and rituximab-based CIT. Berentsen et al. reported a median response duration of 11 months with rituximab monotherapy, suggesting limited durability (17). In contrast, responses appear to be more durable with fixed-duration rituximab-based CIT (18, 19, 22); in a Nordic prospective multicenter study on BR in CAD, the median observed response duration was 32 months (19). During the study period, complement inhibitors were not yet available, and R-CHOP was one of the major CIT options available for untreated WM in Japan (31). In this context, CIT predominated as the first-line therapy in our cohort, including both pCAD and WM-CAS, and durability appeared broadly similar between groups: TTNT was not reached in pCAD and was 39 months in WM-CAS (Log-rank p = 0.1343). The overall response rate was 100% in the pCAD group and 80% in the WM-CAS group; however, these response rates should be interpreted with caution because of the very small sample size. These findings should also be interpreted in the context of historical treatment availability in Japan. Taken together, these results suggest that when hemolysis is the dominant clinical issue and strict categorization is unclear, fixed-duration tumor-directed therapy may be a pragmatic option for both pCAD and WM-CAS.

Patients with CAH are known to have an increased risk of thromboembolic events, likely related to complement activation and hemolysis-associated hypercoagulability (7-9). Furthermore, thromboembolic events may occur regardless of the seasons (9). In an IgM monoclonal gammopathy-associated CAD/cryoglobulinemia series (n=11), transfusion-independent hemoglobin improvement (≥2 g/dL) was achieved in 63.6% of patients; however, mortality remained high (63.6%), potentially related to advanced disease at presentation, associated with a median diagnostic delay of 12 months (6). Accordingly, CIT for CAH requires careful monitoring for thromboembolic and infectious complications. In our cohort, elevated FDP at presentation was more frequent in CAH cases than in WM-only cases, which is consistent with a prothrombotic tendency, whereas no overt thrombotic events were observed. Neutropenia occurred with rituximab-based CIT; however, no grade ≥3 infections were documented.

Limitations

This study is limited by its single-center retrospective design and small sample size, which restricts statistical power and precision for AE and event-time estimates. Molecular stratification was incomplete because an IGHV gene usage analysis (including IGHV4-34) was not performed and *MYD88*^{L265P} testing was missing in one case each of pCAD and WM-CAS, leaving residual diagnostic uncertainty.

Conclusion

In this retrospective single-center cohort, rituximab-based CIT attenuated CAH in both pCAD and WM-CAS, and TTNT was not significantly different between these groups. Although diagnostic overlap remains, particularly among *MYD88*^{L265P}-negative cases, the present results suggest the potential benefit of CIT when CAH is clinically dominant; however, the sample size was small, and further studies are warranted.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Conceptualization, KI, TK, SM, KH, and NS; Methodology, TK and NS; Formal Analysis, KI and NS; Investigation, KI, SM, and KH; Data Curation, KI; Writing - Original Draft Preparation, KI; Writing - Review & Editing, KI, TK, SM, KH, and NS; Supervision, NS; Project Administration, NS. All authors have read and approved the final manuscript.

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Institutional Review Board Statement: 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).

Informed Consent Statement: Informed consent was obtained through an opt-out process on the website, and individuals who declined participation were excluded.

Data Availability Statement: All data generated or analyzed during this study are included in this article. Further inquiries may be directed to the corresponding author.

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