

Histologic Transformation of Waldenström Macroglobulinemia to Diffuse Large B-Cell Lymphoma: Clinical Characteristics, Treatment Patterns, and Outcomes in the Novel Therapy Era

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Background: Histologic transformation of Waldenström macroglobulinemia (tWM) to diffuse large B-cell lymphoma (DLBCL) is traditionally associated with poor prognosis, and optimal management remains unclear. The aim of this retrospective study was to evaluate patient characteristics, disease features, and clinical outcomes of patients with this rare presentation (<5% of cases).

Methods: We analyzed data from all patients (n = 36) at our center with confirmed WM and biopsy-proven DLBCL treated between 6/1990-9/2025. DLBCL response was assessed by Lugano criteria. Progression-free survival (PFS) was defined by progression of either DLBCL or WM. Survival was estimated by Kaplan-Meier and log-rank methods.

Results: Median age at WM diagnosis was 65 years (range: 41-80); 42% were female, and 80% had ECOG performance status (PS) 0-1. International Prognostic Scoring System WM risk was low in 32%, intermediate in 26%, and high in 42% of patients. MYD88, CXCR4 and TP53 mutations were seen in 65% (11/17), 23% (3/13), and 42% (5/12) of evaluable patients at WM diagnosis. Median time from WM to tWM diagnosis was 25.2 months (range 0-213.1); 10 (28%) patients were diagnosed with tWM ≤ 90 days from WM diagnosis. Prior to transformation, 26 patients received WM-directed therapy (median 1 line, range 1-5): anti-CD20 monoclonal antibody (88%), purine analog/alkylator chemotherapy (77%), proteasome inhibitors (42%), and BTK inhibitors (27%).

At DLBCL diagnosis (**Table**), median age was 69 years (range 45-81), 71% had stage III/IV disease, and 86% had PS 0-2. International Prognostic Index (IPI) distribution was 14% 0-1, 57% 2-3, and 29% 4-5. Two patients had double-hit lymphoma, and 5 (14%) had baseline CNS involvement. Frontline DLBCL therapy was R-CHOP in 17 patients (49%), R-EPOCH in 6 (17%), polatuzumab-R-CHP in 3 (9%), and other regimens in 9 (26%); 1 received no therapy (hospice). Twenty-two patients received second-line therapy.

Median follow-up from WM and DLBCL diagnoses, respectively, was 123 and 61.4 months. From DLBCL diagnosis, median overall survival (OS) was 43.5 months, and 2-year OS was 66%. Median frontline PFS was 17.1 months with 2-year PFS of 43%. Two-year PFS was 67%, 54%, and 50% for Pola-R-CHP, R-CHOP and R-EPOCH, respectively, with overlapping confidence intervals. Neither OS nor PFS differed by IPI, stage, or age. PFS after second-line therapy was short (median 6.7 months; 2-year PFS 33%). Seven patients received axicabtagene ciloleucel CAR T-cell therapy (median prior DLBCL and WM treatments = 2 each (range: 1-3 and 0-5, respectively)), with median PFS of 4.8 months, 2-year PFS 43%, and median duration of response 3.8 months.

Conclusions: Despite the advent of novel therapies, including CAR-T, tWM portends a poor prognosis, with no frontline combination appearing superior. The lower 2-year PFS rates with CAR T-cell therapy noted in our study compared with those reported by Durot et al. 2024 (68%) could be due to small sample size, CAR-T product used, or mutational profile differences. Still, further evaluation of T-cell-engaging

approaches, particularly in earlier lines, is warranted. Given the rarity of transformation, these findings provide useful benchmarks requiring multicenter validation in the novel therapy era.

Table: Baseline Characteristics of tWM Cohort at DLBCL Diagnosis.

DLBCL-Related Characteristics	tWM Cohort (n=36)
Age at DLBCL Diagnosis, years	69 (45-81)
ECOG Status, n (%)	
0	6 (20.7%)
1	15 (51.7%)
2	4 (13.8%)
3	3 (10.3%)
4	1 (3.4%)
IPI Score, n (%)	
0	0
1	4 (14.3%)
2	6 (21.4%)
3	10 (35.7%)
4	5 (17.9%)
5	3 (10.7%)
Stage, n (%)	
I/II	10 (29.4%)
III/IV	24 (70.6%)
Laboratory Data	
Hemoglobin, g/dL	10.3 (5.5-16.3)
Absolute Lymphocyte Count, K/uL	0.82 (0.05-11.10)
Beta-2 Microglobulin, mg/L	3.6 (1.3-7.5)
Albumin, g/dL	3.4 (2.5-4.7)
Median Follow-up from DLBCL Diagnosis	61.4 months (95% CI: 53.7-NA months)
Median Follow-up from WM Diagnosis	123 months (95% CI: 110-NA months)

Data presented as median (range) unless otherwise specified. Percentages calculated from patients with available data (ECOG n=29, IPI n=28, stage n=34).

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