Light Chain Amyloidosis in Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma: Treatment Strategies and Outcomes of 74 Cases

N. DANESIN[1,2], A. GUIJOSA[1,3] , T. H. MOUHIEDDINE[1,3], C. EDWARDS[1,3] , S.P.TREON[1,3], J.J.CASTILLO[1,3] and S. SAROSIEK[1,3]

1. Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, Massachusetts, USA
2. Hematology Unit, Department of Medicine, University of Padova, Padova, Italy
3. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA

Dana-Farber Cancer Institute

INTRODUCTION

Light chain (AL) amyloidosis occurs in only 3-7% of patients with Waldenström macroglobulinemia (WM) and is characterized by severe organ dysfunction and poor prognosis.[1]

Given its rarity, large cohorts descriptions and front-line treatments comparisons are limited.

AIMS

- To characterize baseline LPL-related amyloidosis features and assess their prognostic significance
- To evaluate the efficacy of frontline treatment strategies in terms of serum IgM, sFLC, and organ responses
- To describe the impact of Major sFCL/ IgM response on PFS and OS outcomes

METHODS

- Cases of AL/AHL LPL-related referred to DFCI between 2003-2025 were identified and features described at baseline
- AL/AHL diagnosis was made using Congo-red positivity and then confirmed by typing.
- The impact of features on PFS/OS was established with Cox-regression UVA and MVA
- Frontline regimens were grouped into CI (chemoimmunotherapy-based), PI (proteasome inhibitor-based), CI+PI (combined)
- A 6-month landmark analysis from frontline therapy was performed to evalute the impact of Major sFLC/IgM on PFS and OS

CONCLUSIONS

- High incidence of renal, peripheral nervous system, lymph node and cardiac involvement in systemic LPL-related amyloidosis was found.
- The achievement of Major sFLC and IgM response at 6 months predicted higher median OS and PFS,
- CI-, PI- and CI+PI-based frontline regimens showed similar OS and PFS outcomes. IgM, sFLC, organ response were equally distributed.

RESULTS

WM cases (n=72) and non-IgM LPL (n=2) with concurrent AL/AHL amyloidosis were included.

The majority (78%) presented with Mayo 2012 stage I, II disease and only 20% received ASCT consolidation after frontline. Other baseline features are described on Table 1.

Cardiac involvement was an independent predictor of both inferior PFS (HR 3.91) and OS (HR 3.28) while elevated creatinine serum level predicted inferior OS (HR. 2.19).

With a median follow up of 46 months (95% CI, 36.5-73.7), the median PFS was 41.4 months (range, 16.9-109.8) and the median OS was 104.8 months (89.8-NR).
Figure 1 A-B

After landmark analysis, a partial AL response or more at 6 months after treatment initiation portended better median PFS (56.1 vs 1.15 months, p = 0.04) and OS (NR vs 56.7 months, p = 0.02). Similarly, a partial WM response or more at 6 months impacted median PFS (65.8 vs 1.03 months, p < 0.0001) and OS (101.2 vs 48.5 months, p = 0.004). Figure 1 C-F.

CI-based regimens were associated with a better WM response distribution (p=0.03) than PI while no difference in organ response or AL response between CI (n=26), PI (n=26) and CI+PI (n=10) were seen. No significant differences were seen in terms of PFS and OS outcomes. Figure 2.

Patient characteristics	All patients (n= 74)
Age, years Median (IQR)	66 (60-73)
Male, n (%)	48 (65)
Diagnosis, n (%) WM non-IgM LPL	 72 (97) 2 (3)
Chain isotype, n (%) Kappa Lambda Heavy + Light	 23 (31) 42 (57) 9 (12)
Hemoglobin level, g/dL,Median (IQR) (n=72)[a]	12.0 (11.2-13.4)
Platelet count, x10^9/L, Median (IQR) (n=71)[a]	249.0 (195.1-322.3)
B2-microglobulin, mg/L, Median (IQR) (n=46)[a]	3.0 (2.5-4.3)
Serum IgM level, mg/dL, Median (IQR) (n=71)[a]	1768.0 (809.0-2776.0)
dFLC, mg/L, Median (IQR) (n=70)[a]	83.0 (25.5-230.4)
dFLC < 50 mg/L, n (%) (n=63)[a]	23 (37%)
Bone marrow LPL involvement, %, Median (IQR) (n=72)[a]	30 (15-50)
MYD88^{MUT}, n % (n=53)[a]	49 (93%)
CXCR4^{MUT}, n % (n=30)[a]	8 (27%)
[a] Serum creatinine, mg/dL, Median (IQR) (n=71)[a]	0.95 (0.76-1.30)
[a] Serum Albumin, g/dL, Median (IQR) (n=69)[a]	3.7 (3.0-4.1)
Urine protein excretion, mg/24h, Median (IQR) (n=29)[a]	3000 (545-4500)
Alkaline Phosphatase, U/L, Median (IQR) (n=66)[a]	80.0 (65.2-105.4)
Troponin T, ng/L, Median (IQR) (n=53)[a]	11.00 (0.04-37.00)
NT-pro-BNP, pg/ml, Median (IQR) (n=53)[a]	440.0 (138.0-1492.2)
Previous WM treatment, n (%)	25 (34%)
Mayo 2012 score, n (%) (n=58) I II III IV	 24 (42%) 21 (36%) 7 (12%) 6 (10%)
Organ involvement, n (%) Renal Cardiac Peripheral nervous system Lymph nodes Skin/Soft tissue Pulmonary Autonomic nervous system Gastrointestinal tract Hepatic	 30 (41%) 22 (30%) 19 (26%) 17 (23%) 16 (22%) 12 (16%) 8 (11%) 7 (9%) 4 (5%)
ASCT, n (%)	15 (20%)

AL, light chain amyloidosis; AHL, light and heavy chain amyloidosis; IQR, interquartile range; LPL, lymphoplasmacytic lymphoma; dFLC, difference in involved and uninvolved free light chain; MUT, mutated; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WM, Waldenstrom Macroglobulinemia; ASCT, autologous stem cell transplantation.

[a] n = number of patients with available data (missing values excluded).

Table 1. Baseline characteristics at time of AL/AHL diagnosis

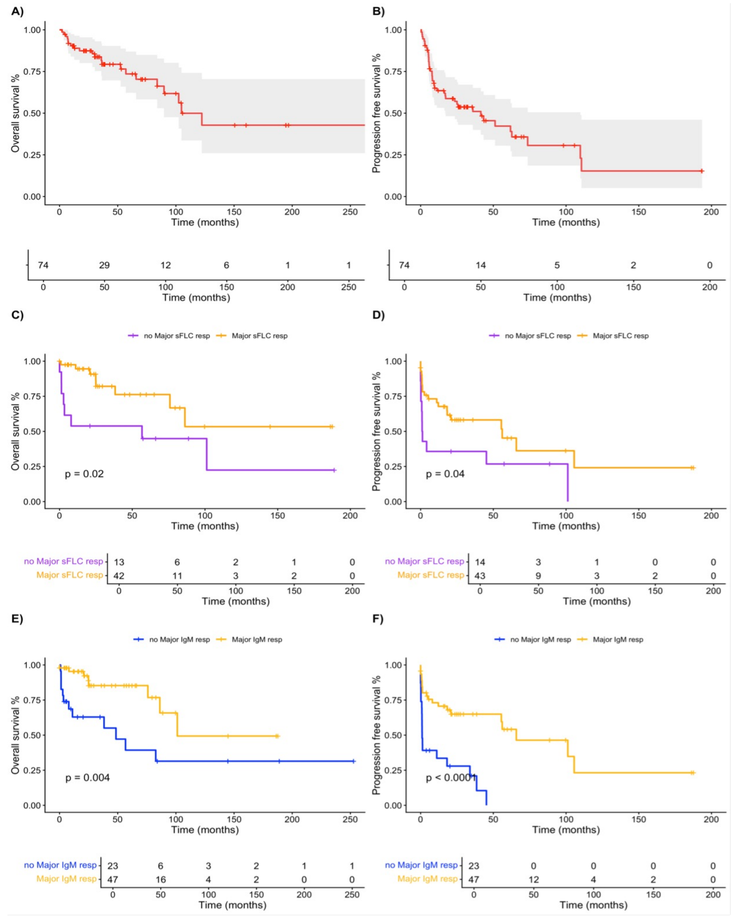

Figure 1. Kaplan-Meier curves for overall survival **(A)** and progression-free survival **(B)** for the entire cohort and clinical subgroups stratified by sFLC response **(C, D)** and IgM response **(E,F)**

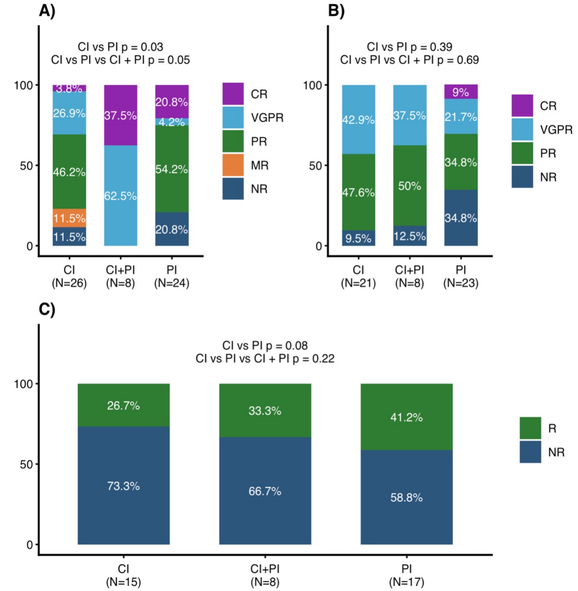

Figure 2. Hematologic and organ responses after frontline therapy. A) Hematologic response based on serum IgM, **B)** Hematologic response based on serum free light chains, **C)** Organ response. R = responder, NR = not responder.

ACKNOWLEDGEMENTS

WMR Fund, the Kaplan Family Fund for Waldenström Macroglobulinemia, the Bayer Family Research Fund, the Fred and Michelle Brettschneider Family Research Fund, the Deborah Cummins Waldenström Memorial Fund, and the Vanier Family WM Research Fund.

CONTACT INFORMATION

nicolo.danesin@aopd.veneto.it; shayna_sarosiek@dfci.harvard.edu

REFERENCES

1 **Merlini G et al**. Report of Consensus Panel 6 from the 11 th International Workshop on Waldenström's Macroglobulinemia on Management of Waldenström's Macroglobulinemia Related Amyloidosis. *Semin Hematol. 2023 Mar;60(2):113–7.*