

A REAL-LIFE MULTICENTER STUDY ON BEHALF OF THE FONDAZIONE ITALIANA LINFOMI INVESTIGATING RENAL DYSFUNCTION IN WALDENSTRÖM MACROGLOBULINEMIA: CLINICAL OUTCOMES AND MANAGEMENT STRATEGY.

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Renal impairment in Waldenström Macroglobulinemia (WM) may be lymphoma-related or unrelated. We have retrospectively analyzed a cohort of 464 WM patients - from 17 Italian Fondazione Italiana Linfomi-affiliated centers - who received a first-line treatment between 2000 and 2023. We compared the clinical characteristics and outcomes of patients without and with renal dysfunction, defined as creatinine clearance at diagnosis < 60 ml/min/1,73m². Sixty-nine patients were excluded due to the absence of complete data. A sub-analysis was done distinguishing cases with and without biopsy-proven renal involvement.

The 116/395 WM patients with renal dysfunction displayed more advanced median age (76 vs 67 years, $p < 0.0001$), lower median Hemoglobin (10.8 vs 11.8 g/dL, $p = 0.008$) and higher median 24h proteinuria levels (0.29 vs 0.20 g, $p = 0.04$). Cumulative Illness Rating Scale (CIRS), comorbidities such as hypertension, diabetes, urothelial malignancies and therapy regimens and responses did not differ between the two subgroups. The histopathological patterns identified in 25 renal biopsies out of the 116 cases with renal dysfunction were: amyloidosis (40%), tubulo-interstitial infiltration (20%), other lesions (16%), non-cryoglobulinemic-glomerulonephritis (GNF) (12%), combined non-cryoglobulinemic-GNF and light chain deposition disease (8%), cryoglobulinemic-GNF (4%). Survival outcomes were similar considering the biopsied subgroup as compared to the not biopsied one in both the entire and the renal dysfunction cohorts. Patients with renal dysfunction showed an inferior median overall survival (OS) (139 vs 203 months, $p < 0.0001$) and median progression free survival (PFS) (80 vs 106 months, $p = 0.0018$) with a trend to inferior time to next treatment (TTNT) (23 vs 33 months, $p = 0.07$) (Figure1). The cumulative incidence of progression events was higher in the subgroup with renal dysfunction both at 100 (38% vs

28%) and 200 (58% vs 52%) months after diagnosis ($p = 0.049$). In univariate Cox-regression analysis, older age (HR 1.03, $p = 0.04$), first line therapy with Bendamustine-Rituximab (BR) alone (HR 0.4, $p=0.002$) and first line therapy with both Rituximab-Cyclophosphamide-Dexamethasone and BR taken together (HR 0.58, $p=0.04$) were prognostic factors for PFS in patients with renal dysfunction. In the renal dysfunction subgroup, BR as first-line therapy displayed higher median PFS as compared to other regimens (109 vs 53 months, $p=0.002$).

Furthermore, to better understand the impact of advanced age on renal dysfunction, the subcohorts of younger and older patients ($<70y$ and $\geq 70y$) were analyzed separately. In the younger subgroup we found that patients with renal dysfunction displayed worse median PFS (80 vs 121 months, $p=0.01$) whereas no difference was found in the older one (78 vs 80 months, $p=0.43$). A positive renal biopsy was associated with worse median PFS in under 70y WM patients with renal dysfunction according to Cox-univariate analysis (HR 5.51, $p=0.02$).

In conclusion, renal dysfunction portends a worse PFS, OS and TTNT outcomes in WM. BR seems to be a valid first-line therapeutic option in this setting. WM patients younger than 70y at diagnosis displayed shorter PFS when renal dysfunction is present and especially when is confirmed by biopsy. Prospective multicenter studies, including larger cohorts of renal-biopsied patients, are needed to confirm these findings.

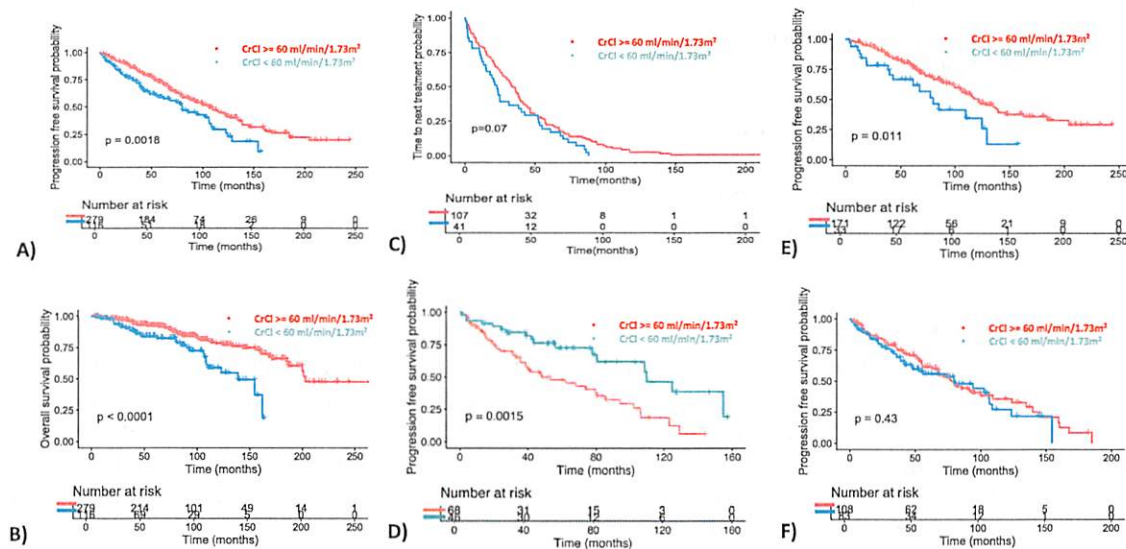


Figure 1. A) Progression free survival B) Overall survival C) Time to Next Treatment, comparing WM patients with CrCl < 60ml/min/1.73m² and CrCl ≥ 60 ml/min/1.73m² D) Progression Free Survival comparing WM patients with CrCl < 60 ml/min/1.73m² treated with or without Bendamustine-Rituximab as first line therapy E) Progression free survival of WM patients under 70 and over 70 F) at diagnosis divided in CrCl < 60ml/min/1.73m² and CrCl ≥ 60 ml/min/1.73m²

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To the IWWM:

Dear IWWM Committees,

As Mentor of Dr. Nicolò Danesin, it is for me a great pleasure to endorse his participation to the 12th International Workshop on Waldenström's Macroglobulinemia, which will be held in Prague (Czech Republic) on 17-19th October 2024.

Dr. Danesin graduated in Medicine and Surgery at the University of Padua under my tutorship in 2022, and since then he has committed himself towards performing clinical and translational research in WM.

Nicolò is a talented and enthusiastic Hematologist in training. He has contributed to the analysis of our WM patients' cohort and his efforts led him to publish a major paper in the journal "Hemasphere" in late 2023 (Danesin N et al Hemasphere 2023 Oct 3;7(10):e964. doi: 10.1097/HS9.0000000000000964) and then two other papers in "Annals of Hematology" (Danesin N et al. Ann Hematol 2024 Apr 30 doi: 10.1007/s00277-024-05770-4.) and in "Cancer Reports" early in 2024 (Danesin et al 2024 Apr;7(4):e2062. doi: 10.1002/cnr2.2062).

His main research interests are WM, and particularly the elderly population, the renal involvement and the correlation between cytogenetic alterations and molecular and clinical features of the disease, as well as other indolent lymphomas.

We are delighted to present at the 12th IWWM in Prague the early results of a study that we have designed, and which is led by Dr. Danesin, aimed at assessing the impact of renal involvement and renal impairment in WM, This study started in Italy under the sponsorship of Fondazione Italiana Linfomi (FIL) and is now recruiting patients from all across many FIL centers.

Hoping to find Your acceptance, I send you my kindest regards.

Sincerely Yours,

Prof. Francesco Piazza
University of Padova

