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Letter
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Waldenström Macroglobulinemia in Very Elderly (≥75-year-old) Patients: A 33-year-retrospective Cohort Study in an Italian University Hospital

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Waldenström macroglobulinemia (WM) is a rare indolent non-Hodgkin lymphoma characterized by the expansion in the bone marrow of monoclonal IgM (mIgM)-secreting lymphoplasmacytic cells.[1–3] Many patients live with WM during the elderly age experiencing comorbidities that must be considered in the management of the disease. Age ≥65 years at the start of therapy portends a worse outcome, according to the international prognostic scoring system on Waldenström macroglobulinemia (IPSSWM) and revised-IPSSWM (r-IPSSWM).[4] However, survival and baseline characteristics of WM patients who are ≥75 years old at diagnosis (very elderly) have been scarcely described in clinical trials and population-based studies.[5–7] Zanwar et al[8] reported an inferior cause-specific survival for the ≥75-year subgroup of WM patients but other studies have demonstrated a higher mortality rate due to WM-unrelated conditions mostly represented by coexisting malignancies[7] or noncancer-related disorders.[9] Indeed, a higher cumulative incidence of other malignancies in WM has been reported.[10–12] More recently, an inflammatory variant of WM has been described[13] apparently characterized by worse disease features and survival outcomes as compared with noninflammatory WM.[14] The epidemiology of this form and the role of secondary causes of chronic inflammation and conditions affecting mortality in very elderly WM patients are still debated issues.

In the present study, we aimed at comparing clinico-biological features (including those related to inflammation) and survival outcomes (event-free survival [EFS] and overall survival [OS]) in a cohort of WM patients stratified by age ≥75 and <75 years. More details on methods are described in the Supplemental Digital Content (SDC). The study was carried out after approval of the Ethic Committee of Azienda Ospedaliera University of Padova (protocol 4089/AO/17).

One-hundred and fifty-three patients diagnosed with WM between 1990 and 2022 were retrospectively reviewed and included in the study. For the entire cohort, median age at diagnosis was 66.0 years (interquartile range [IQR], 56.0–73.0) and median follow-up time since diagnosis was 6.1 years (IQR, 3.4–11.5), while for the untreated subcohort was 6.8 years (IQR, 3.7–11.8). Eleven of the 153 (7.2%) patients were lost during follow-up. Baseline patients' characteristics of the 2 subcohorts (<75 and ≥75 years) are described in Table 1.

Thirty-three of 153 (21.6%) patients belonged to the very elderly group. They displayed a higher frequency of renal dysfunction compared with younger patients (42.4% versus 25.0%, respectively; $P = 0.05$) and a trend toward the coexistence of other tumors (37.9% versus 22.3%, respectively; $P = 0.09$). The frequency of peripheral neuropathy was similar between the 2 subgroups. Twenty-eight of 153 (18.3%) patients displayed anti-MAG antibodies, 7 of 28 (25%) versus 21 of 28 (75%), respectively, for the ≥75 and <75 years groups.[3] The very elderly subcohort showed a trend toward higher levels of mIgM and significantly higher levels of β_2-microglobulin and lower levels of albumin (mIgM: 17.6 g/L versus 11.7 g/L, $P = 0.08$; β_2-microglobulin: 4.1 mg/L versus 2.9 mg/L, $P = 0.04$; albumin: 37.6 g/L versus 41.3 g/L, $P = 0.02$). Cytogenetic analysis was performed in 64% (98/153) of patients. In 37.7% (37/98), the karyotype was altered and deletion of 6q (6q-) was the most frequent abnormality (29.7%). The relative frequency of complex karyotypes (≥3 alterations) was 29.7% (11/37) of the cases found altered by karyotyping and 11.2% (11/98) of all analyzed cases. The very elderly patients displayed more frequently clonal cytogenetic aberrations (69.6% versus 29.5%; $P = 0.001$) with similar distribution of complex karyotypes (25% and 33%; $P = 0.3$). No statistically significant difference was found in other WM-related features.

No significant differences between the 2 subcohorts were observed in terms of need of therapy (63.6% versus 58.5%; $P = 0.46$), dose intensity, and/or cycles' number reductions in

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Table 1

Univariate Analysis of Variables Associated With the ≥75 and <75-year-old Patients Groups Stratified at Diagnosis

	≥75 Y (n = 33)	<75 Y (n = 120)	*P*-value
Clinical variables			
Male, n (%)	14/22 (63.6)	81/120 (67.5)	0.72
Lymphadenopathy or splenomegaly, n (%)	13/31 (41.9)	66/116 (56.9)	0.14
Neuropathy, n (%)	6/33 (18.2)	27/118 (22.9)	0.56
Amyloidosis, n (%)	2/33 (6.0)	5/118 (4.2)	0.65
CAS, n (%)	1/33 (3.0)	1/118 (0.8)	0.39
Renal dysfunction, n (%)	14/33 (42.4)	29/116 (25.0)	**0.05**
Hypertension, n (%)	10/33 (30.3)	42/116 (36.2)	0.53
Diabetes, n (%)	2/33 (6.0)	7/116 (6.0)	1.00
Other neoplasia, n (%)	11/29 (37.9)	25/112 (22.3)	0.09
Therapy, n (%)	21/32 (63.6)	69/118 (58.5)	0.46
First-line therapy modifications, n (%)	7/20 (35.0)	16/64 (25.0)	0.38
IPSSWM score, n (%)			
Low		22/60 (36.7)	
Intermediate	7/14 (50.0)	20/60 (33.3)	0.24
High	7/14 (50.0)	18/60 (30.0)	0.13
WM-related deaths, n (%)	4/19 (21.0)	1/7 (14.0)	0.70
Biological variables			
Hemoglobin, g/L, median (IQR)	117.0 (98.00–132.00)	119.5 (97.75–138.00)	0.38
Platelets, $\times 10^9$/L, median (IQR)	243.0 (204.00–283.00)	226.5 (174.75–306.75)	0.58
Neutrophils, $\times 10^9$/L, median (IQR)	3.6 (2.95–4.66)	3.7 (2.86–4.70)	0.86
Monoclonal component IgM, g/L, median (IQR)	17.6 (13.06–25.13)	11.7 (6.09–21.70)	0.08
β_2-microglobulin, mg/L, median (IQR)	4.1 (2.56–5.14)	2.9 (2.22–3.83)	**0.04**
Albumin, g/L, median (IQR)	37.6 (33.83–40.84)	41.3 (37.42-43.35)	**0.02**
LDH, U/L, median (IQR)	149.5 (132.50–199.00)	194.0 (137.00–256.50)	0.08
CRP, mg/L, median (IQR)	8.7 (2.90–20.00)	5.7 (2.90–13.35)	0.55
FLC ratio κ/λ, median (IQR)	2.8 (0.59–11.26)	3.0 (1.14–7.69)	0.65
Bone marrow infiltration fraction, median (IQR)	0.45 (0.18–0.75)	0.35 (0.20–0.70)	0.79
Cytogenetic/molecular variables			
MYD88 L265P, n (%)	23/24 (95.8)	58/67 (85.3)	0.28
CXCR4 S338X, n (%)	1/11 (10.0)	10/34 (41.6)	0.25
Cytogenetic aberrations, n (%)	16/23 (69.6)	21/71 (29.5)	**0.001**
Complex karyotype, n (%)	4/16 (25.0)	7/21 (33.3)	0.58

Statistical significance was considered for *P* value <0.05 (bold values).

CAS = cold agglutinin syndrome; CRP = C-reactive protein; FLC = free light chain; IPSSWM = international prognostic scoring system on Waldenström macroglobulinemia; IQR = interquartile range; LDH = lactate dehydrogenase; WM = Waldenström macroglobulinemia.

first-line therapy (35.0 % versus 25.0%; *P* = 0.38) and first-line therapy regimens adopted and responses (Table 1; Suppl. Figure S1; Suppl. Figure S2). The overall response rate (ORR) to first-line therapy was 65% (5% minor response [MR], 40% partial response [PR], 15% very good partial response [VGPR], and 5% complete response [CR]) in the very elderly group compared with 80% (7% MR, 51% PR, 15% VGPR, and 7% CR) in the younger cohort. As expected, the ORR for patients managed with chemotherapy only was lower than that for patients treated with anti-CD20 plus chemotherapy, 42.9% versus 80.6%, respectively. Elderly patients displayed a higher rate of progressing disease (20% versus 5%; *P* = 0.001). Expectedly, they also showed a trend toward being distributed in the intermediate (by age) and high IPSSWM risk groups. Overall, 54 of 90 (60%) of the WM patients treated received only first-line therapy, while 36 of 90 (40%) received 2 or more lines. Median time from first- to second-line treatment was 35.4 months (IQR, 15.3–71.6). First-line therapeutic regimen more frequently administered in very elderly and in younger WM patients was Rituximab-Bendamustine (47.6% and 39.5%).

The median OS and EFS (Suppl. Figure S3) of the entire WM cohort were 198 months (95% confidence interval [CI], 186 months to not reached) and 164 months (95% CI, 115 months to 198 months), respectively. Median OS and EFS were shorter in the very elderly as compared with younger patients: 79 months (95% CI, 79 months to not reached) versus. 198 months (95% CI, 186 months to not reached) with a log-rank *P* = 0.008 (Suppl. Figure S4); median EFS not reached (95% CI, 45 months to not reached) versus 166.0 months (95% CI, 125 months to not reached) with a log-rank *P* value = 0.02 (Figure 1). In univariate Cox proportional hazards regression analysis, no WM-related clinical characteristics were found to impact OS outcome with statistical significance in very elderly patients (Suppl. Table S1). Of the WM patients evaluable for specific cause of death (26/30), 5 of 26 (19.2%) died due to WM lymphoma progression or complications and 21 of 26 (80.8%) due to WM-unrelated causes. In the latter subgroup, the majority died of second malignancies (5/21) or infections including COVID-19 (6/21). The prevalence of WM-related deaths between the 2 age-stratified subgroups maintained a similar distribution, namely 21% (4/19) in ≥75-year old versus 14% (1/7) in younger patients (*P* = 0.70). At variance, univariate analysis revealed a worse EFS in patients aged ≥75 years that correlated with the presence of neuropathy (hazard ratio [HR], 5.77 [95% CI, 1.11-30.05]; *P* = 0.03), wild type MYD88 (HR, 0.05 [95% CI, 0.003-0.75]; *P* = 0.03), and elevated β_2-microglobulin (HR, 1.30 [95% CI, 1.04-1.59]; *P* = 0.02). Interestingly, we observed a trend toward a worse EFS associated with lower serum albumin levels (HR, 0.8 [95% CI, 0.62-1.04]; *P* = 0.09) and elevated C-reactive protein (CRP) blood concentrations (HR, 1.04 [95% CI, 0.99-1.09]; *P* = 0.06) (Suppl. Table S2). In multivariate analyses, none of the considered features resulted to be independently linked with significance to inferior EFS and OS in the very elderly group.

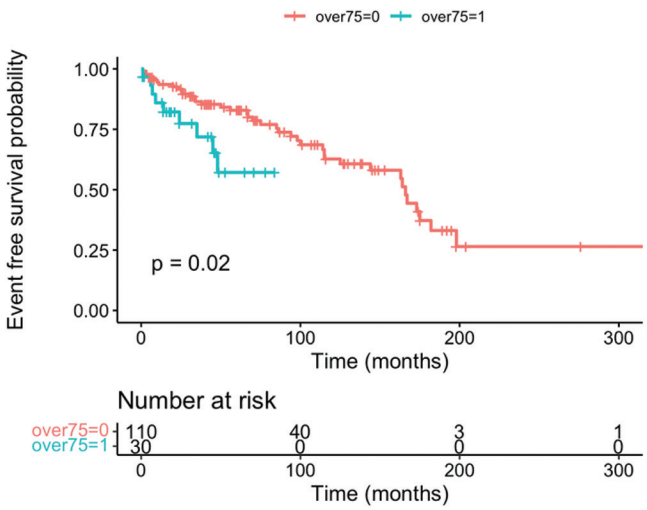

Figure 1. EFS curves of the 2 subgroups (≥75 and <75-years old at diagnosis) of WM patients. EFS = event-free survival; WM = Waldenström macroglobulinemia.

The present study is one of the first analysis that focused on the very elderly patients affected by WM. This population, despite being frequently managed in daily clinical practice, has been scarcely investigated in clinical trials and very scant real world data exist describing the features of WM in patients aged >75 years.

We found that at diagnosis elderly WM patients display different characteristics as compared with the younger ones. They had higher blood concentrations of mIgM and β_2-microglobulin and lower concentrations of albumin. Elevated β_2-microglobulin could also depend on the higher prevalence of impaired renal function in the older subcohort. Interestingly, cytogenetic aberrations and WT-MYD88 were more frequent in elderly patients. Other important features were equally prevalent in the 2 subcohorts. Remarkably, even if the anti-MAG antibodies-associated peripheral neuropathy accounted for the most frequent cause of peripheral neuropathy in both age-stratified subgroups, as we and others described,[15,16] univariate analysis showed that it correlated with an inferior EFS outcome in the very elderly subcohort. The same correlation with inferior EFS was observed for high β_2-microglobulin levels and WT-MYD88, while elevated CRP and low albumin blood levels displayed a trend toward statistical significance.

High β_2-microglobulin and CRP and low albumin levels may reflect an inflammatory WM.[13] It has been proposed that inflammatory status may play a role only in the reduced median time to next treatment, while different studies suggested an inferior median OS in inflammatory WM due to higher prevalence of del6q.[14] Our findings indicate that in elderly WM, some clinical features are possibly correlated with an inflammatory status and may associate with an inferior EFS. We also observed that the 2 age-stratified cohorts received similar first-line therapeutic regimens with comparable dose intensity/density. Response rates were also comparable, except for more frequent progressive disease rate in the elderly. These findings suggest that therapy modifications marginally influence the observed inferior EFS and OS outcomes in WM older patients.

Analyzing the potential causes of death, very elderly patients displayed higher incidence of second malignancies. However, we could not identify neither WM-related nor WM-unrelated (including other neoplasia) features—among those recorded—associated with statistical significance to a worse OS outcome. Thus, it is likely that other causes, not included in our dataset could have impacted the OS outcome in the elderly population.

The monocentric retrospective type of analysis, the follow-up time duration, and the sample size are the limitations of this study. However, the results obtained could contribute to add information in an underexplored subset of WM patients and likely to promote further multicentric studies.

AUTHOR CONTRIBUTIONS

FP envisioned the work, FP and LT clinically supervised WM patients' management, supervised the research, and FP wrote the article. ND, MLS, and GS collected data, analyzed data, and wrote the article. AG provided statistical advice and revised the article. MR, TB, AB, AV, MC, LP, SM, FV, CG, CB, and RZ provided clinical data from patients and supervised clinical management. LB, AM, and RB performed the cytogenetic and molecular analyses.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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