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RESEARCH ARTICLE

Younger patients with Waldenström Macroglobulinemia exhibit low risk profile and excellent outcomes in the era of immunotherapy and targeted therapies

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Abstract

We analyzed 160 young Waldenström Macroglobulinemia (WM) patients with a median age of 49 years (range 23-55 years), diagnosed between January 2000 and January 2019 in 14 Italian centers. At diagnosis, 70% of patients were asymptomatic. With a median follow-up of 5.6 years, 57% have been treated. As initial therapy 79% of patients received chemo-immunotherapy, 13% a chemo-free induction and 8% chemotherapy only. At relapse or progression, 6% underwent an autologous

stem cell transplantation. Overall, 19% of patients received ibrutinib during the course of the disease. According to IPSSWM, 63% were classified as low risk, 27% as intermediate risk and 10% as high risk. Five-year OS was shorter in high-risk as compared with low or intermediate risk patients (92.9% vs 100% P = .002). According to revised IPSSWM, 92% were classified as very low or low risk and 8% as intermediate risk, with a shorter 5-year OS in the latter group (87.5% vs 100%, P = .028). The OS of young WM patients was not significantly reduced as compared with age-matched, sex-matched and calendar year-matched general population. Early diagnosis, absence of high-risk features in symptomatic patients and high efficacy of modern treatments are the main determinants of the excellent outcome of young WM patients.

1 | INTRODUCTION

Waldenström Macroglobulinemia (WM) is a rare indolent lymphoma typical of the elderly population, with a median age at diagnosis of approximately 70 years and a slight male predominance.[1] Age is the most important prognostic factor in WM, and unrelated mortality significantly impacts survival in older patients.[2-4] The International Prognostic Scoring System for WM (IPSSWM), the most validated prognostic tool so far, stratifies WM patients into three risk groups based on age, hemoglobin and platelet count, serum β_2-microglobulin and serum monoclonal IgM values.[2] This prognostic score was developed 10 years ago in a cohort of patients mostly treated with chemotherapy, with only 4% of patients having received rituximab as part of their initial treatment. The past two decades have witnessed important treatment advances in WM, with the introduction of chemo-immunotherapy in the early 2000s and then of ibrutinib. Due to treatment advances, the survival of WM patients diagnosed since 2000 has significantly improved.[4,5] A revised international prognostic score system for Waldenström's macroglobulinemia (rIPSSWM) including age, albumin, serum β_2-microglobulin and LDH, has been recently developed in a large cohort of WM patients mainly treated with rituximab-based chemo-immunotherapy, or with proteasome inhibitors as primary therapy.[3] Both IPSSWM and rIPSSWM were developed in typical WM populations, with a median age close to 70 years. Based on the National Cancer Institute's Surveillance Epidemiology, and End Results (SEER) database, in the United States less than 10% of WM patients are younger than 50 years at diagnosis.[6] Few studies have addressed the clinical presentation, patterns of treatment and outcome of young WM patients treated in the era of immunotherapy and targeted therapies. The aims of this study were: (a) to assess the pattern of treatment, including the proportion of patients treated frontline with immunotherapy-containing regimens, the proportion of patients receiving ibrutinib and the proportion of patients undergoing autologous transplantation; (b) to assess whether the ISSWM and r-IPSSWM are able to stratify young WM patients treated with modern approaches; and (c) to evaluate the life expectancy of young WM patients as compared with calendar-matched, age-matched and sex- matched general population.

2 | MATERIALS AND METHODS

2.1 | Patients

The study included WM patients diagnosed between January 2000 and January 2019 in 14 hematologic centers across Italy, who were ≤55 years-old at the time of diagnosis. The cut-off of 55 years was selected based on a similar cut-off used to define young patients in other lymphoproliferative disorders typical of the elderly population, such as chronic lymphocytic leukemia.[7,8] The diagnosis of WM was made using criteria established during the second International Workshop on WM, which were retrospectively applied to patients diagnosed before 2003.[9] Baseline demographics and clinical factors, time to first treatment, type of initial therapy, date of progression after front-line therapy and survival were retrieved from clinical records. Response to therapy was assessed using the sixth IWWM criteria.[10] The overall survival of patients included in the study was compared with the expected survival of the general Italian population matched by sex, age, and calendar year. Relative survival was obtained by dividing the overall survival after diagnosis observed in the study population by the expected survival of the sex and matched general population. The expected survival estimates were calculated utilizing Italian life tables (Istituto Nazionale di Statistica, ISTAT). The study was approved by the Ethics Committee of the coordinating center. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000, and subjects provided informed consent.

2.2 | Statistical analysis

Patients' characteristics were summarized using median and interquartile range (IQR) for continuous variables and absolute and relative frequencies for categorical variables. Fisher's exact test was used to estimate the association between two categorical variables. The comparison of quantitative variables between two independent groups of patients was evaluated by the Mann-Whitney two-sample test. Time to first treatment was defined as the time between diagnosis and the date of initiation of treatment or date of last follow-up. The cumulative incidence of second malignancies was estimated with a competing risk approach, accounting for death from any cause as the competing event. Overall survival (OS) was defined as

time from diagnosis to death due to any cause or last follow-up time, whichever occurred first. The effect of treatment on OS was estimated analyzing the treatment as a time-dependent covariate. Expected survival was calculated using the Ederer II method, with estimates based on ISTAT tables. The *P* values <.05 were considered statistically significant. All statistical analyses were conducted using the Stata 16 software (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC).

3 | RESULTS

The study cohort included 160 young WM patients, 43 (27%) diagnosed between 2000 and 2009 and 117 (73%) between 2010 and 2019. The median age of patients was 49 years (range 23-55). Their clinical characteristics at diagnosis are reported in Table 1. The MYD88 (L265P) mutation was detected using allele-specific polymerase chain reaction in 79 of 84 patients tested (94%).

3.1 | Time to first treatment and characteristics of first-line therapy

At the time of diagnosis, 49 out of 160 patients (31%) were symptomatic and required immediate treatment, whereas 111 were initially asymptomatic (69%). After a median follow-up of 5.6 years (IQR 2.7-8.8), 91 of 160 patients (57%) have been treated. The median treatment-free survival (TFS) was 43 months, with 5-year TFS of 45.3% (95% CI 36.6-53.7) (Figure 1A). Seventy-two of 91 patients (79%) received chemo-immunotherapy frontline: chemotherapy consisted of alkylator-based regimens in 35 patients of 71 cases (49%), bendamustine in 21 (30%) and purine analogs in 15 (21%). After induction with chemo-immunotherapy, two patients received rituximab maintenance every 2 months for 2 years. Twelve patients of 91 (13%) received a chemo-free induction consisting of rituximab as single agent (eight patients), rituximab in combination with bortezomib and dexamethasone (two patients) or in combination with ibrutinib (two patients). Seven out of 91 patients (8%) received chemotherapy (mainly oral chlorambucil) without monoclonal antibodies. The overall response rate (ORR) to induction therapy was 81%, including 38% complete remission (CR) or very good partial remission (VGPR). Six of 91 patients (6%) received an autologous stem cell transplantation at relapse or progression. Five-year PFS after transplant was 20%. Overall, 17 of 91 patients (19%) received ibrutinib during the course of their disease (two as initial therapy and 15 at relapse).

3.2 | Prognostic stratification of young WM patients according to IPSSWM and rIPSSWM and outcome

Both IPSSWM and rIPSSWM were available respectively for 82 and 60 symptomatic patients receiving therapy. According to IPSSWM prognostic score, 52 patients (63%) were classified as low risk, 22 (27%) as intermediate risk and eight (10%) as high risk. No deaths were observed in the low and intermediate risk patients, whereas the 5-year OS was shorter in high-risk patients (92.9% vs 100% *P* = .002).

TABLE 1 Clinical presentation of 160 young WM patients included in the study

Clinical characteristic	Number of patients evaluated	Result
Age at diagnosis (y), median (range)	160	49 (23-55)
Male/female, number of patients (%)	160	106 (66%)/54 (34%)
Familial history of WM or related disorders, number of patients (%)	157	19 (12%)
Prior diagnosis of MGUS, number of patients (%)	145	73 (50%)
Lymphoadenopathy, number of patients (%)	159	30 (19%)
Splenomegaly, number of patients (%)	159	19 (12%)
Extranodal disease, number of patients (%)	156	6 (4%)
Peripheral neuropathy, number of patients (%)	160	16 (10%)
Amyloidosis, number of patients (%)	149	1 (1%)
Immune thrombocytopenia, number of patients (%)	160	2 (1%)
Cold agglutinin disease, number of patients (%)	118	4 (3%)
ALC ($\times 10^9$/L), median (IQR)	121	2.2 (1.70-2.8)
Hb (g/dL), median (IQR)	158	13 (11-14.2)
PLT ($\times 10^9$/L), median (IQR)	153	265 (210-317)
LDH (U/L), median (IQR)	131	218 (151-296)
Serum β2-microglobulin (mg/L), median (IQR)	132	2.2 (1.8-2.9)
Serum M-protein (g/L), median (IQR)	133	16 (8-25)
Serum albumin (g/L), median (IQR)	120	41 (37-44)
IgG levels (mg/dL), median (IQR)	140	932 (680-1193)
IgA levels (mg/dL), median (IQR)	139	98 (57-157)
IgM levels (mg/dL), median (IQR)	145	1785 (890-3141)
k/λ ratio, median (IQR)	63	2.2 (1.3-6.7)
BJ proteinuria, number of patients (%)	144	56 (39%)
Median bone marrow infiltration (%) (IQR)	145	30 (20-60)

Abbreviation: MGUS, monoclonal gammopathy of undetermined significance; ALC, absolute lymphocyte count; LDH, lactate dehydrogenase; M-protein, monoclonal protein; Ig, immunoglobulin; BJ, Bence-Jones.

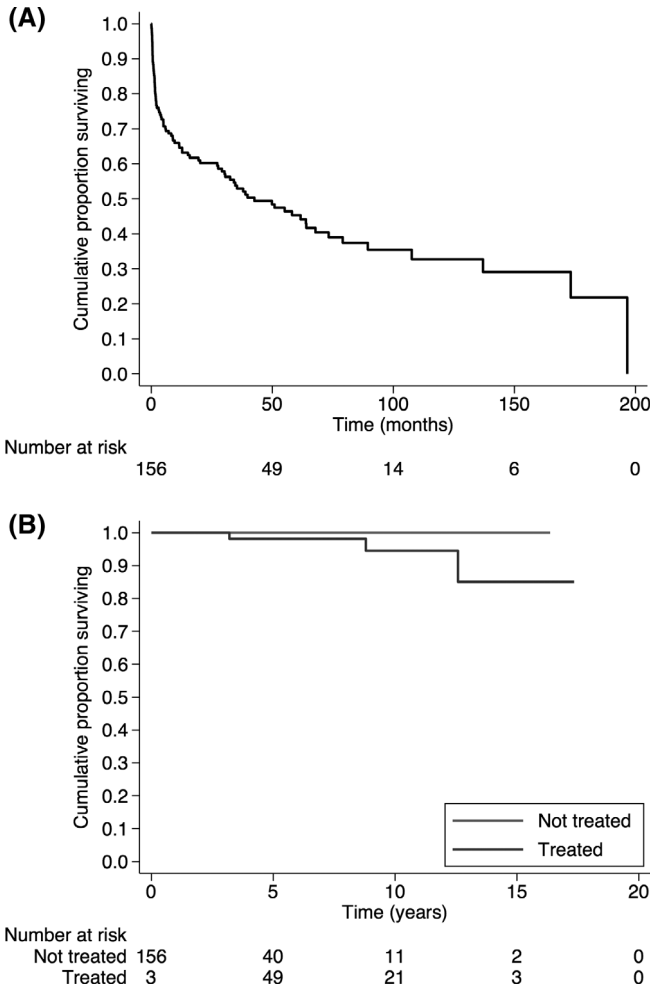

FIGURE 1 A, Treatment-free survival in the study cohort of patients, B, Overall survival of treated or untreated patients, analyzing treatment as a time-dependent covariate

According to revised rIPSSWM, 27 patients (45%) were classified as very low risk, 28 (47%) as low risk and five (8%) as intermediate risk, none of the patients was classified as high or very-high risk. The 5-year OS was shorter in intermediate risk patients as compared with low or very low risk ones (87.5% vs 100%, $P = .028$). In order to assess the impact of risk factors other than age, we sought to evaluate the frequency of risk factors considered in the IPSSWM and rIPSSWM in our series. Interestingly, hypoalbuminemia and increased serum β_2-microglobulin were observed less frequently in young WM patients, suggesting that the better risk profile of young patients is attributable not only to age but also to a different distribution of other risk factors (Table 2).

3.3 | Outcome of patients

During follow-up, five of 160 patients (3%) developed a solid cancer (n = 2) or a second hematologic malignancy (myelodysplastic syndrome n = 2, diffuse large B-cell lymphoma n = 1). Four of them had been previously treated with alkylators or purine analogs. Using a competing-risk approach, the cumulative incidence of second cancers was 1.9% at 5 years and 7.5% at 10 years. We did not find a significance difference in the incidence of second cancers between treated and untreated patients ($P = .290$). Three patients have died, two of WM and one of acute myeloid leukemia secondary to myelodysplastic syndrome. The 5-year and 10-year OS from diagnosis were 99% and 97% respectively. As treatment may impact survival, either as a result of more advanced disease, or due to potential treatment-related toxicity, we performed a time-dependent survival analysis, considering therapy as a time-dependent covariate, and found that the OS of treated and untreated WM patients was not significantly different (5-year OS 98.2% vs 100%, $P = .140$) (Figure 1B). No differences in OS were observed between patients diagnosed in the period 2000-2009 and 2010-2019 ($P = .213$). The OS of young WM patients was not significantly reduced as compared with age-matched, sex-matched and calendar year-matched general population. Ten-year relative survival was 1.01 (95% confidence interval: 0.95-1.01) (Figure 2).

TABLE 2 Distribution of risk factors in symptomatic WM patients included in this study as compared with IPSSWM and revised IPSSWM studies

Characteristic	Frequency		
	Present study	IPSSWM study[2]	rIPSSWM study[3]
Hb <11.5 g/dL, % of patients	60%	60%	NR
Platelets ≤100 × 10^9/L, % of patients	14%	9%	12%
Serum β_2-microglobulin >3 mg/L, % of patients	33%	56%	77%
LDH ≥250 U/L, % of patients	28%	NR	15%
Albumin <3.5 g/dL, % of patients	22%	36%	40%
Serum M-protein >7 g/dL, % of patients	2%	7%	NR

Abbreviation: NR, not reported.

4 | DISCUSSION

In this study we analyzed WM patients aged ≤55 years, diagnosed and treated in the last two decades. Young WM patients represent less than 10% of all cases and are underrepresented in clinical trials and in observational studies aimed at evaluating prognosis. We included in the analysis only patients diagnosed since 2000, when rituximab became widely available in Italy, to provide information on the outcome of patients treated with modern approaches. Although a comparison with older WM patients was beyond the scope of this study, the clinical presenting features as well as the rate of MYD88 (L265P) mutation in young WM patients included in this study are mostly consistent with those described in older patients.[11] Of note, a higher number of cases was diagnosed in the second decade as compared with the first one. As there is no evidence of an increased

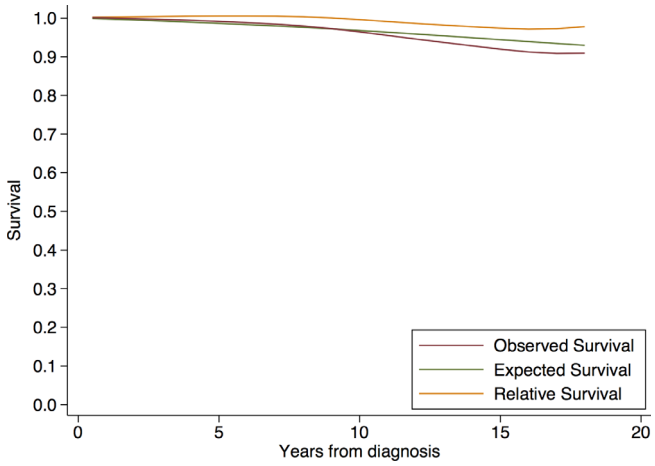

FIGURE 2 Expected, observed and relative survival of young WM patients

incidence of WM from epidemiological studies, our hypothesis is that more diagnoses have been made in the last decade as a result of increasing disease awareness and increasing tendency to perform bone marrow biopsies in the diagnostic work-up of young patients with a serum IgM monoclonal gammopathy, albeit asymptomatic. This hypothesis is supported by the higher proportion of asymptomatic WM patients observed in this study as compared with previous reports.[12,13]

The first aim of the study was to assess the pattern of treatment, including the proportion of patients treated frontline with immunotherapy-containing regimens, the proportion of patients receiving ibrutinib and the proportion of patients undergoing autologous transplantation during the course of their disease. Overall, the majority of patients included in this study were treated according to the most updated recommendations of the International Workshop on WM consensus panel.[14] We found that 79% of young WM patients received chemo-immunotherapy frontline. Our findings compare favorably with a large, observational, retrospective study conducted in Europe, including symptomatic WM patients treated between 2000 and 2014, where 43% of patients were initially treated with monotherapy, mostly chlorambucil, and only 36% had received chemo-immunotherapy in the front-line setting.[6] Only 13% of patients included in our study received a chemo-free treatment frontline. Although omitting chemotherapy is clearly appealing in young patients, there are no randomized studies demonstrating the superiority of chemo-free regimens over standard chemo-immunotherapy. Some ongoing trials are trying to address this important issue. Long-term effects of treatment, including the development of second cancers, are a concern especially in young patients. In a previous study, we reported a 10-year cumulative incidence of 18% of second cancers in WM patients.[16] Other groups found similar results in the United States.[17] The lower incidence of second cancers observed in this study is not unexpected, as the incidence of the most common cancers increases with aging, but the limited exposure to chlorambucil may have played a role. Actually, in a randomized study comparing fludarabine with chlorambucil the incidence of second cancers was significantly higher in the latter group.[18]

Despite young age, a minority of patients underwent autologous stem cell transplantation (ASCT) at relapse. Note, ASCT is considered a valuable option for salvage in WM, particularly among younger patients with chemo-sensitive relapse. In a study from the European Bone Marrow Transplant Registry (EBMTR) that included 155 WM patients receiving autologous stem cell transplantation, the 5-year PFS was 49% and the non-relapse mortality was 5.6%.[15] Due to the lack of phase III randomized trials, the choice between ASCT and a continuous therapy with ibrutinib is still an open issue in young WM patients relapsing after an initial chemo-immunotherapy.

Another aim of this study was to evaluate the performance of the available prognostic scores (IPSSWM and r-IPSSWM) in young WM patients. Both scores, in fact, were developed in WM patients with a median age close to 70 years and identified age as the most impactful prognostic factor. In our study, the majority of patients were classified as low risk with IPSSWM and as very low or low risk with r-IPSSWM. Only 10% of symptomatic patients were classified as high-risk according to the IPSSWM, and none was at high or very high risk according to r-IPSSWM. These findings indicate a lower performance of existing prognostic scores in young WM patients and suggest the need of an age-adjusted prognostic model for their risk stratification.

We are aware that this study has some limitations: first, the retrospective design may have biased some results; secondly, the limited number of deaths reduces the power of survival analyses.

Taking into account these limitations, our study indicates that the life expectancy of young WM patients diagnosed in the last two decades is comparable to that of the age and sex matched general population. Early diagnosis, reflected by the high proportion of asymptomatic patients, the absence of high-risk features in symptomatic patients and the high efficacy of modern treatments are the main determinants of the excellent outcome of young WM patients.

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M.V. designed the research and wrote the manuscript; C.K. and V.V.F. performed statistical analyses; A.F., AMF, R.R., M.M., F.P., M.M., G.B., L.L., S.F., M.G., V.D.F., A.A., P.M., N.F., M.D., I.D., C.G., A.C. collected and analyzed data; C.V., S.L., L.A. critically revised the manuscript. All authors reviewed and approved the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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