American Journal of Hematology AJH

RESEARCH ARTICLE | Full Access

Survival trends in young patients with Waldenström macroglobulinemia: Over five decades of experience

Karan L. Chohan, Jonas Paludo, Nishanth Vallumsetla, Dirk Larson, Rebecca L. King, Rong He, Wilson Gonsalves, David Inwards, Thomas E. Witzig, Abhisek Swaika, Tania Jain ... See all authors

First published: 01 January 2023 | https://doi.org/10.1002/ajh.26807

Karan L. Chohan and Jonas Paludo are co-first authors.

Volume 98, Issue 3
March 2023
Pages 432-439

Abstract

Waldenström macroglobulinemia (WM) is a rare, indolent lymphoma, that predominately affects the elderly. We report the outcomes of young WM patients, evaluated over five decades, compared to their older counterparts, matched for the time of diagnosis. Between January 1, 1960 and October 31, 2013, 140 (11.8%) WM patients were ≤50 years of age at diagnosis in our database, and their estimated 10-year overall survival (OS) was 74%, with death attributable to WM in a higher proportion of patients compared to their older (≥65 years) counterparts (91% vs. 58%, *p* = .0001). Young patients were grouped into three cohorts based on the timing of the initiation of therapy: Group 1 (1960–1977, *n* = 12), Group 2 (1978–1995, *n* = 48), and Group 3 (1996–2013, *n* = 74). Among young patients, there was no disease-specific survival (DSS) difference across the three periods, [median DSS at 13 years (95% CI 5–23), 16 years (95% CI 14–22), and 15 years (95% CI 10-NR; *p* = .41), respectively]. However, DSS for the older cohort incrementally improved (Group 1, median 5.2 years, Group 2: 9.6 years, Group 3: 12 years; *p* = .05) over these periods. The estimated average years-of-life lost for the young cohort was 11.2 years from diagnosis, based on the expected survival for a normal age- and sex-matched population. Despite a protracted disease course, nearly all young patients succumb to their disease. In contrast to the improved survival of the elderly patient population, the evolving treatment strategies in WM have not impacted the outcome of young patients; however, the impact of Bruton tyrosine kinase inhibitors on this unique patient population remains to be determined.

1 INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare, low-grade B-cell non-Hodgkin lymphoma characterized by bone marrow involvement with clonal lymphoplasmacytic cells and immunoglobulin (Ig) M monoclonal gammopathy.[1, 2] WM has an overall annual age-adjusted incidence of 3.8 cases per million-person years, with a male predominance, and the median age at diagnosis of approximately 73 years.[3, 4] The natural history of WM is not well defined due to the indolent course of the malignancy that predominantly afflicts the elderly, who are already typically burdened with advanced age-related comorbidities.[5, 6]

Age is a major prognostic factor in WM and has been repeatedly used in different staging systems. Patients who are 50 years or younger comprise less than 10% of the patient population.[7, 8] This unique subset has generally fewer comorbidities and competing causes of death, and is therefore better suited for an accurate evaluation of the disease course.[9] Overall, there are very few studies assessing the outcomes of the younger WM population, and the available data are confounded by a potential overestimation of survival owing to the inclusion of patients with smoldering WM.[10] Furthermore, with the evolution of therapy over the past few decades from chemotherapy-based to immunotherapy-based regimens, there has been limited work assessing the impact of changing therapeutic approaches on the outcomes of younger patients with WM.[11] More recently, Bruton tyrosine kinase inhibitors (BTKi) have been incorporated into the management of WM and shown to successfully rescue patients with disease refractory to rituximab and/or conventional chemotherapies.[12, 13] However, as WM is an indolent malignancy, the long-term impact of BTKi that have become only recently available, would be discernible later this decade with extended follow-up.

We evaluated the outcome of young WM patients compared to a time of diagnosis matched cohort of older patients over a protracted period. The aims of this study were to: (1) assess the differences in the baseline characteristics between younger and older matched WM patients and (2) determine the impact of changing therapies, over the course of the last five decades on the outcome of young patients, specifically in comparison to the matched older cohort.

2 METHODS

This study was approved by the Mayo Clinic Institutional Review Board in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability guidelines. We included patients with biopsy-proven WM who were assessed between January 1, 1960 and October 31, 2013 at the Mayo Clinic. Cases were defined as subjects with a confirmed diagnosis of WM who were 50 years or younger at the time of diagnosis, an age cutoff previously used in the WM literature.[14] The older control cohort included subjects with a confirmed diagnosis of WM who were 65 years or above at the time of diagnosis. The matching was done in a 1:1 ratio by the time of the diagnosis of WM. Medical records of the cases and the controls were reviewed for demographic data, family history, clinical features, treatment characteristics, and outcomes.

Familial WM was defined as patients who had 1st or 2nd-degree relatives with WM or another clonal B-cell disorder. The patients who did not receive therapy within 6 months of the diagnosis were assumed to have smoldering WM (SWM) at diagnosis.[15] The $MYD88^{L265P}$ mutation status was recorded when available and assessed by the amplification-refractory mutation system (ARMS), a variant of allele-specific polymerase chain reaction (AS-PCR), with an analytical sensitivity of approximately 1% mutation detection in a wild-type background from bone marrow aspirate samples. The International Prognostic Scoring System (IPSS) for WM, based on five variables (hemoglobin ≤11.5 g/dl, platelet count $\leq 100 \times 10^9$/L, β2-microglobulin >3 mg/L, serum monoclonal IgM >7.0 g/dl and age > 65 years), was calculated at the time of initial therapy.[8]

The patients were grouped into three cohorts of approximately equal time periods based on the timing of initiation of frontline therapy: Group 1 (1960 to 1977), Group 2 (1978 to 1995), and Group 3 (1996 to 2013). The overall survival (OS) was calculated by the Kaplan Meier analysis, from the time of initiation of frontline therapy until the date of last follow-up or death by any cause. Patients who were alive at the date of the last follow-up were censored at the date of the last follow-up for the calculation of OS. The disease-specific survival (DSS) was calculated from the time of commencement of frontline therapy until the date of the last follow-up or death related to WM. Patients who were alive at the date of last follow-up or died from causes unrelated to WM were censored at the date of last follow-up for the calculation of DSS. Time from the initiation of frontline therapy was selected for survival analysis as our study attempted to specifically assess the value of evolving treatment strategies. The cause of death was considered WM-related if death resulted from progressive disease, amyloidosis-related end-organ failure, transformation to diffuse large B-cell lymphoma (DLBCL), infections, or treatment-related complications, including therapy-related myelodysplastic syndrome (t-MDS). Death was considered unrelated if the patient died while WM was in remission, off therapy and death occurred from causes unrelated to WM (e.g., stroke, myocardial infarction, or another unrelated cancer), without evidence of disease progression or relapse. The average years-of-life-lost, based on identical gender and age, was calculated using the United States total population and estimated using the Kaplan–Meier method by subtracting the area under the observed survival curve from the area under the expected survival curve for a normal age and gender-matched population, where both curves were calculated out to 30 years. The survival curves were compared using the log-rank test. Findings were tested for statistical significance using Fisher's exact test and Kruskal-Wallis tests. A *p*-value <.05 was considered statistically significant. Missing data were handled by comparing clinical outcomes between the group with the data variable available, against the group with data missing. If both groups had statistically comparable outcomes, the data was presented, excluding those with unavailable data. The analysis was performed using JMP 10.0 software (SAS Institute, Cary, North Carolina).

3 RESULTS

3.1 Patient characteristics

Of 1180 patients with WM seen during this 53-year period, 140 (11.8%) were 50 years or younger at the time of diagnosis and categorized as cases. The median age at diagnosis for the 140 cases was 45 (range 30–50) years, with a male to female ratio of 1.6. The median age at diagnosis for the 140 time-of-diagnosis matched older patients in the control group was 73 (range 65–85) years, with a male to female ratio of 1.1. Among the patients with a documented family history (young *n* = 128; older *n* = 99), familial WM was seen in 17 (13%) of the younger patients and 9 (9%) of older patients, *p* = .40. The baseline characteristics of the case and control groups are outlined in Table 1. In patients with hyperviscosity syndrome (younger *n* = 23; older *n* = 2), the following associated symptoms were observed: headache (younger *n* = 6; older *n* = 1), shortness of breath (young *n* = 3; older *n* = 0), dizziness/lightheadedness (young *n* = 3; older *n* = 1), and fundoscopic abnormalities (young *n* = 9; older *n* = 1).

TABLE 1. Baseline patient characteristics at WM diagnosis

Parameter [a]	Younger cohort (*n* = 140)	Older cohort (*n* = 140) [a]	*p* value
Age at diagnosis, years	45 (30–50)	73 (65–85)	
Hemoglobin, g/dl	10.2 (5.4–15.7)	10.4 (4.8–15.3)	.23
Platelets, ×10⁹/L	222 (59–543)	225 (21–634)	.58
B2 microglobulin, mcg/ml	2.5 (0.7–9.3)	3.5 (1–17)	**.02**
IgM, mg/dl	4466 (24–14 400)	2820 (19–13 900)	**.0002**
BM involvement, % (range)	45 (5–90)	30 (5–95)	.59
Splenomegaly, *n* (%)	22 (31)	10 (12)	**.004**
Lymphadenopathy, *n* (%)	29 (39)	19 (22)	**.03**
Hyperviscosity symptoms, *n* (%)	23 (46)	2 (7)	**.0003**
Family history [b], *n* (%)	17 (13)	9 (9)	.40
Median DSS, years			
Group 1	13 y (95% CI: 5–23; 10-y DSS 81%)	5.2 y (95% CI: 4–9; 10-y DSS 0%)	**.02**
Group 2	16 y (95% CI: 14–22; 10-y DSS 80%)	9.6 y (95% CI: 5–13; 10-y DSS 43%)	**.006**

Note: Signficant p values are indicated in bold.

[a] % Calculated taking into account the missing data for each parameter.

[b] 1st and 2nd degree relative with history of WM of other B-cell lymphoma.

[c] Nucleoside analogue: fludarabine, cladribine, pentostatin; alkylators: chlorambucil, melphalan, cyclophosphamide, bendamustine; proteasome inhibitor: bortezomib.

Within the younger cohort, 5 (4%) patients had CNS involvement by WM (Bing-Neel syndrome), 4 (3%) patients were diagnosed with AL amyloidosis, and 3 (2%) presented with a von Willebrand factor abnormality. Among the older cohort, 8 (6%) patients were diagnosed with AL amyloidosis, and one patient presented with a von Willebrand factor abnormality, but Bing-Neel syndrome was not identified. Symptoms of peripheral neuropathy were observed in 19 (14%) patients in the younger cohort and in 12 (9%) in the older cohort. Adjusted by age, the IPSS score was similar in the younger (≤1 risk factor: 78%; 2 risk factors: 17%; ≥3 risk factors: 5%) and older (≤1 risk factor: 77%; 2 risk factors: 22%; ≥3 risk factors: 1%) cohorts, *p* = .19.

Smoldering WM at diagnosis was observed in 30 (21%) patients in each cohort. The time from diagnosis to the initiation of first-line therapy in patients with SWM who progressed to active WM was comparable in the young [median 2.4 years (95% CI: 2–4.4)] and older cohorts [median 2 years (95% CI: 1.5–3.8), *p* = .41]. MYD88 mutation status was available in 28 (18 younger, 10 older) patients. $MYD88^{L265P}$ mutation revealed a similar prevalence in younger (*n* = 13/72%) and older (*n* = 10/100%) patients with WM, *p* = .06.

The baseline characteristics for each group according to the commencement of frontline therapy are shown in Table 2. Group 1 (1960–1977) was composed of 25 (9%) patients, Group 2 (1978–1995) had 92 (34%) patients and Group 3 (1996–2013) had 151 (57%) patients.

TABLE 2. Baseline group characteristics

	Group 1 (1960–1977) *n* = 25 (9%)	Group 2 (1978–1995) *n* = 92 (34%)	Group 3 (1996–2013) *n* = 151 (57%)	*p*-value
Young cohort, median (range)	*n* = 12 (9%)	*n* = 48 (36%)	*n* = 74 (55%)	
Hemoglobin, g/dl	8 (6.5–14)	10.6 (6.1–14.9)	10.2 (5.4–15.7)	.07
Platelets, ×10⁹/L	192 (59–297)	208 (91–543)	227 (73–501)	.40
B2 microglobulin, mcg/ml	-	-	2.62 (0.7–9.34)	-
IgM, mg/dl	4380 (270–11 900)	4800 (61–12 000)	4245 (24–14 400)	.45
BM involvement, %	-	35 (5–80)	50 (5–90)	.34
Older cohort, median (range)	*n* = 13 (10%)	*n* = 44 (33%)	*n* = 77 (57%)	
Hemoglobin, g/dl	9.6 (4.8–14.8)	9.7 (6.7–14.3)	10.9 (6.8–15.3)	.02
Platelets, ×10⁹/L	184 (35–496)	216 (21–634)	237 (47–482)	.35
B2 microglobulin, mcg/ml	-	-	3.5 (1.5–8.6)	-
IgM, mg/dl	309 (102–2240)	4100 (228–13 900)	2810 (19–8740)	.004

[a] Nucleoside analogue: fludarabine, cladribine, pentostatin; alkylators: chlorambucil, melphalan, cyclophosphamide, bendamustine; proteasome inhibitor: bortezomib. BM, bone marrow; R, rituximab.

3.2 Survival outcomes

The median follow-up for the young and the older cohorts was 11.6 years (95% CI: 8–14) and 11 years (95% CI: 10–13), respectively. The estimated median OS from frontline therapy was 15.4 years (95% CI: 12.7–18; 10-year OS of 74%) for the young patients and 7.2 years (95% CI: 5–8; 10-year OS of 31%) for the older patients, *p* = .0001. The estimated median DSS from frontline therapy for the young cohort was 15.6 years (95% CI: 13–21; 10-year DSS of 77%) compared to 11.1 years (95% CI: 8–12.6; 10-year DSS of 51%) for the older cohort, *p* = .0003 (Figure 1A). At the time of analysis, 50 (36%) patients in the young cohort had died, with 91% of deaths related to WM. In the older cohort, 88 (63%) patients had died, with 57% of deaths related to WM, *p* <.0001.

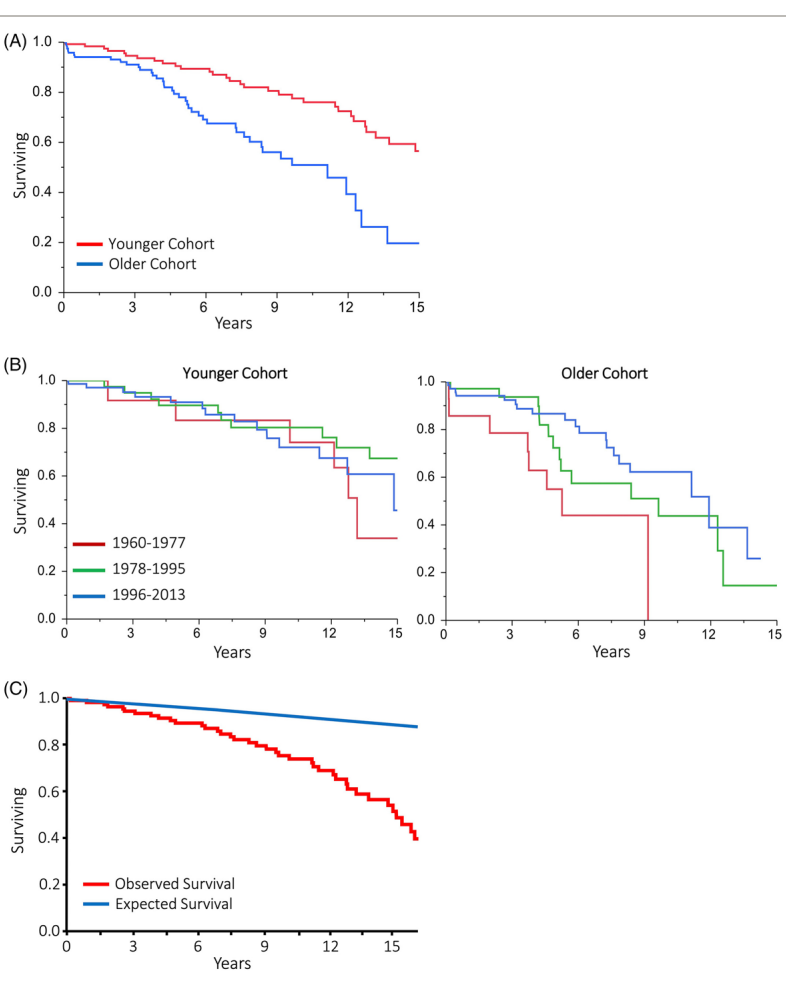

FIGURE 1 Open in figure viewer | PowerPoint

Disease specific survival from frontline therapy (A). Disease specific survival from frontline therapy for Group 1, 2 and 3 (B). Observed vs expected survival from frontline therapy in the younger cohort (C). [Color figure can be viewed at wileyonlinelibrary.com]

Table 1 and Figure 1B demonstrate the DSS for the different groups in the young and older cohorts. In the young cohort, no significant improvement in DSS was seen over time (*p* = .41). However, an incremental improvement in DSS was noted in the older cohort of patients (*p* = .05). For young WM patients, the average years-of-life lost were estimated at 11.2 years from the date of diagnosis (Figure 1C).

3.3 WM-directed therapy

During the follow-up, 137 (98%) young patients and 135 (96%) older patients required WM-directed therapy. The frontline therapy administered in the young and older cohorts is shown in Table 1. The frontline therapy by the decade of commencement of treatment is shown in Figure 2. Utilizing the IPSS score as the marker of baseline patient characteristics, the differences among the IPSS scores within the older and younger patient subcohorts categorized by the treatment received were assessed. For older patients, there was no significant difference among the IPSS scores (*p* = .78) within the subcohorts receiving frontline treatment with rituximab-based regimens (*n* = 47; IPSS 2: 32%, IPSS 3: 68%), chlorambucil-based regimens (*n* = 66; IPSS 2: 35%, IPSS 3: 65%), nucleoside-analogue (NA) regimens (*n* = 7; IPSS 2: 43%, IPSS 3: 57%), and other regimens (*n* = 13; IPSS 2: 46%, IPSS 3: 54%). Similarly, for the younger patients, there was no significant difference among the IPSS scores (*p* = .15) within the subcohorts receiving frontline treatment with rituximab-based regimens (*n* = 51; IPSS 1: 73%, IPSS 2: 20%, IPSS 3: 8%), chlorambucil-based regimens (*n* = 48; IPSS 1: 94%, IPSS 2: 6%), NA regimens (*n* = 15; IPSS 1: 87%, IPSS 2: 13%), and other regimens (*n* = 19; IPSS 1: 79%, IPSS 2: 16%, IPSS 3: 5%).

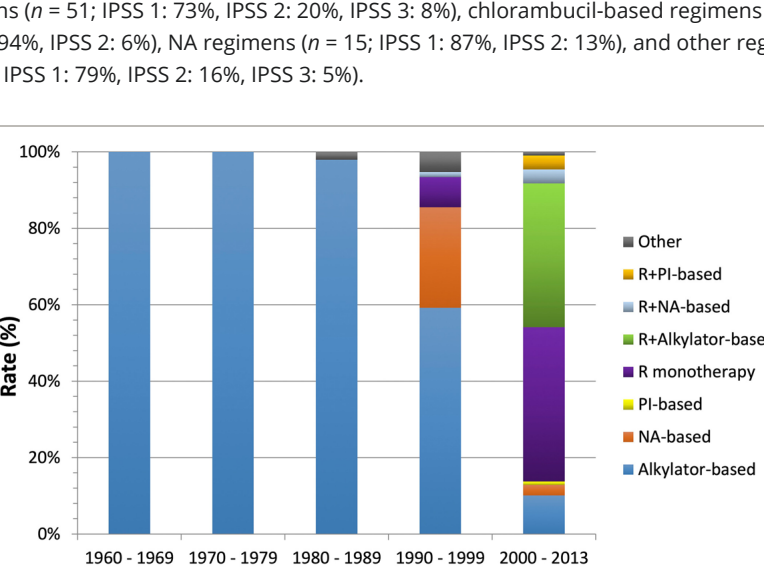

FIGURE 2 Open in figure viewer | PowerPoint

Frontline chemotherapy by decade of therapy initiation. NA, nucleoside analogue; PI, proteasome inhibitor; R, rituximab. Nucleoside analogues: fludarabine cladribine, pentostatin; alkylators: chlorambucil, melphalan, cyclophosphamide, bendamustine; Proteasome inhibitor: bortezomib. [Color figure can be viewed at wileyonlinelibrary.com]

Frontline alkylator-based regimens were associated with worse DSS in older WM patients (median 8.3 years [95% CI: 5.6–12]) compared to young WM patients (15.8 [95% CI: 12–21]), *p* = .002. Within the older cohort, the use of frontline chlorambucil-based regimens led to a poorer DSS (median 7.6 years [95% CI: 5.2–12]) compared to non-chlorambucil alkylator-based regimens (i.e., cyclophosphamide and bendamustine) (median 13.7 years [95% CI: 8.3-NR], *p* = .03) although no differences between the baseline characteristics as assessed by the IPSS scores of the two subcohorts was observed (*p* = .17). No such DSS difference was seen in young patients treated with frontline chlorambucil versus non-chlorambucil alkylator-based regimens (median 16 [95% CI: 12.2–21] vs. 15.6 years [95% CI: 7.6-NR], *p* = .62) despite a higher proportion of baseline IPSS 2 and 3 scores (*n* = 10/31%) in the subcohort receiving frontline chlorambucil versus non-chlorambucil alkylator-based regimen (*n* = 4/8%, *p* = .006).

Frontline NA regimens were associated with a median DSS of 11.1 years (95% CI: 7.8-NR) in older patients compared to 15.4 years (95% CI: 11.4-NR) in younger patients, *p* = .40. Within the older cohort, a trend towards a longer DSS was observed with frontline NA-based regimens (median 11 years [95% CI: 7.8-NR]) compared to alkylator-based regimens (median 7.6 years [95% CI: 5.1–9.6], *p* = .06). Such a trend was not evident in young WM patients, in whom the median DSS with frontline NA-based regimens was 16 years (95% CI: 12–21) compared to 15.4 years (95% CI: 11.4-NR) with alkylator-based regimens, *p* = .79.

Frontline rituximab-based therapy was administered in 52 (38%) younger patients, with no difference seen in the DSS in young patients treated with a frontline rituximab-based regimen (median 15.6 years [95% CI: 9.6-NR]) compared to young patients treated with other regimens (median 16 years [95% CI: 13–22], *p* = .37). However, a longer DSS was observed in the older cohort when frontline regimens incorporated rituximab (median 12.3 [95% CI: 8.3-NR] vs. 8.4 years [95% CI: 5.2–12], *p* = .04) compared to other regimens. The DSS of older patients treated with a rituximab-based regimen in the frontline setting was comparable to that of the young patients (median 12.3 years [95% CI: 8.3-NR]; 10-year DSS 66% vs. median 15.6 years [95% CI: 9.6-NR]; 10-year DSS 70%), respectively, *p* = .45.

In the young cohort, 11 patients underwent autologous stem cell transplantation (ASCT) as a salvage approach after a median of 3.5 regimens (range 1–8). The median DSS from ASCT was 4.2 years (95% CI: 0.8-NR). Three patients underwent allogeneic stem cell transplant as part of salvage therapy, two for relapsed/refractory WM and one following the development of t-MDS. The median DSS from an allogeneic transplant was 8 years (95% CI: 7.1–10). In the older cohort, only two patients underwent ASCT; the median DSS was not reached.

In the young cohort, transformed aggressive lymphoma and t-MDS were diagnosed in 7 (6%) and 4 (3%) patients, respectively. Of the four patients diagnosed with t-MDS, three had prior exposure to NA [median 5.4 years (range 3.7–8.3) from NA exposure to t-MDS diagnosis] and one to single-agent chlorambucil and subsequently single-agent cyclophosphamide, 12.7 years prior to the diagnosis of t-MDS. Of the seven patients in the young cohort whose WM transformed to a higher-grade lymphoma, the observed OS after transformation was 1.1 years (95% CI, 0.2–2.2).

4 DISCUSSION

As a malignancy predominately affecting elderly patients, data highlighting the clinical characteristics and impact of WM on younger patients are very limited.[16] However, one in four WM patients is younger than 60 years[17] and one in 10 is 50 years or younger at diagnosis as shown by our data. In the general population, the estimated incidence of moderate to severe comorbidities at 50 years of age is only 18% in the United States[9] and the life expectancy at 50 years of age is an additional 32 years.[18] With a long life expectancy ahead of them and no significant comorbidities, WM can potentially take a substantial toll on this young (≤50 years of age) patient population. The available data in young WM are sparse and conflicting.[15, 16] Our study is the most comprehensive report on the clinical characteristics and outcomes of a large young WM (≤50 years) patient population spanning over five decades. It compares the outcomes of a sizable cohort of young WM patients to a matched older WM patient cohort (≥65 years) over a protracted time interval. Overall, although major advances have occurred in the management of WM, significant survival improvement for young WM patients has not yet been witnessed. Despite an indolent disease course, almost all young patients succumb to their disease, and unfortunately, have an average years-of-life lost are estimated at 11.2 years from diagnosis.

The proportion of smoldering WM, the median time from diagnosis to initiation of frontline therapy, and the age-adjusted IPSS score at the time of therapy initiation were similar among both older and younger WM patients. However, at the time of diagnosis, young WM patients presented with higher rates of lymphadenopathy, splenomegaly, hyperviscosity symptoms, and serum IgM levels. These findings were present despite the absence of significant differences in familial WM, previously shown to present with higher IgM levels.[19] It is possible that, given the greater organ and functional reserve, younger patients are better able to compensate for the physiologic demands of the disease, presenting later with more advanced features.[9] In addition, all the cases of Bing-Neel syndrome observed in our cohort were in the younger patient group. We hypothesize this may be partially explained by younger patients living long enough to develop CNS involvement; however, given the few patients who developed the syndrome, this should be further corroborated in future studies.

Previous studies have analyzed the impact of MYD88 and CXCR4 mutational status on the clinical manifestations of WM.[20, 21] $MYD88^{WT}$ is associated with higher rates of splenomegaly, and $MYD88^{L265P}CXCR4^{WT}$ is associated with a higher rate of lymphadenopathy. $CXCR4^{WHIM}$ mutations, especially nonsense mutations, are associated with higher IgM levels and hyperviscosity. Data regarding patients' CXCR4 mutational status were unavailable in our study. Albeit, not statistically significant, likely due to the small sample size, a higher proportion of patients harboring the $MYD88^{WT}$ genotype was seen in the subset analysis of the younger cohort. While we cannot definitively draw any meaningful conclusions, an early signal in the current study warrants further exploration in this area. Indeed, two studies focusing on cohorts with the $MYD88^{WT}$ signature have demonstrated a lower median age among this patient sub-population.[21, 22] Furthermore, patients with SWM who harbor $MYD88^{WT}$ genotype have previously demonstrated a trend toward a shorter time-to-progression to active WM, perhaps contributing to the enrichment of the younger patient population with this genetic signature.[23]

With respect to the study that analyzed the survival of patients with WM using the SEER database[17] from 1991 to 2010, we observed a longer median OS (11.1 years vs. 7 years) and 10-year OS rates (53% vs. 39%) in our patient population. However, when considering only the older cohort (≥65 years) from our study, the median OS (7.2 years) and 10-years OS (31%) were comparable.[17] These discrepancies are potentially related to referral bias to a tertiary center, to which the fitter, and oftentimes, younger patients are able to travel. The 10-year OS (74%) observed in younger patients from our study was lower than that of an Italian study (97%) of young (≤55 years) WM patients,[24] likely due to the evaluation of a more recent cohort (2000–2019) in the latter study which also included patients receiving BTKi-based regimens. As expected, in our study, younger WM patients had significantly longer OS and DSS compared to the older patient group, over five decades, likely in the context of overall better functional reserve and fewer comorbidities.[9] Interestingly, only approximately half of the deaths in the older WM group were WM-related, compared to almost all deaths in younger patients being WM-related. However, despite the longer survival as compared to older patients, the estimated years-of-life lost (11.2 years) highlights the profound impact of WM on younger patients' overall life expectancy.

This improvement in the DSS among older patients may be in part attributable to the improvement in non-WM-related care, mainly advances in supportive care and the management of comorbidities, and in turn, a gain in life expectancy in the backdrop of improved WM-directed therapies.[11] Younger patients, with fewer competing causes of mortality and comorbidities, may benefit less from these factors, succumbing to WM-related causes. This lack of DSS improvement among young patients has been observed in a SEER database study where no improvement in OS was seen among patients diagnosed from 2001 to 2010 compared to 1991 to 2000.[17] Although not addressed in our study, changes in WM management over the time period may have had an impact on other aspects of patient care, including quality of life and improved tolerability of therapy, that may not directly have a noticeable impact on survival.

During the timeframe of the study, the widely practiced approach of frontline use of rituximab, either as monotherapy or in combination with other agents, did not show a significant survival advantage compared to older conventional chemotherapy in the younger cohort. However, in the older cohort, frontline rituximab-based regimens were associated with a survival improvement that closely matched the DSS seen in young WM patients. Frontline chlorambucil-based regimens showed a somewhat worse effect on the DSS of older patients, but not in the young cohort, attesting to the fact that frontline therapy may impact patient outcomes even in an indolent disease such as WM with a relapsing–remitting course. A trend towards longer DSS was seen with the use of frontline NA-based regimens. These findings substantiate the results of a phase 3 trial comparing frontline chlorambucil and fludarabine in WM patients with a median age of 68 years, demonstrating inferior OS with chlorambucil (median OS 5.8 years) versus fludarabine (median OS NR, *p* = .014).[25] When compared to frontline alkylator-based regimens, NA-based regimens demonstrated a trend toward a longer DSS in the older cohort. ASCT, when performed as salvage therapy in a small number of younger WM patients, showed promising results, suggesting that it could be a viable option for relapsing patients who are more likely to be ASCT eligible. However, NAs, although an option for aggressive disease control, are not recommended as frontline regimens for the young, potentially transplant-eligible candidates, who are typically best served by avoiding stem-cell-toxic drugs that can adversely affect stem cell mobilization and potentially lead to second malignancies.[26-28] Among the patients in the younger cohort who developed t-MDS (*n* = 4) during the study period, 75% had received a prior NA-based regimen.

Assessing limitations, we acknowledge that the retrospective study design allows for a greater influence of confounding variables, missing data, and bias. However, given the indolent nature of WM and the rarity of this malignancy, especially among young patients, prospective studies with a large cohort of patients would be exceedingly difficult to conduct. Secondly, it is important to highlight that patient outcomes may be influenced by the center where patients are treated.[29] The outcomes observed in our large-volume, academic tertiary referral center may not be generalizable to other centers. Lastly, our study only assessed patients up to 2013, when the BTKi were not available.[13] As more options, including BTKi and BCL2 inhibitors with established efficacy, are routinely incorporated into the management of patients with WM, it is possible that we may start observing an appreciable improvement in outcome even among young patient populations.

In summary, although major advances in the treatment of WM have occurred over the last several decades and survival outcomes have improved for WM patients, significant improvement in the survival of the younger WM population has not been evident so far. This population deserves special attention, particularly in the design, and planning of future studies and management algorithms.

CONFLICT OF INTEREST

None.

REFERENCES