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Disease outcomes and biomarkers of progression in smouldering Waldenström macroglobulinaemia

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Summary

Patients with asymptomatic/smouldering Waldenström macroglobulinaemia (SWM) have a variable risk of progression to active WM. Our study evaluated 143 patients with SWM consecutively seen between January 1996 and December 2013. With a median [95% confidence interval (CI)] follow-up of 9·5 [8·1–11·5] years, the cumulative rate of progression was 11% at 1 year, 38% at 3 years and 55% at 5 years. On multivariate analysis, haemoglobin (Hb) ≤123 g/l [risk ratio (RR) 2·08; $P = 0·009$] and β_2-microglobulin (β_2M) ≥2·7 μg/ml (RR 2·0; $P = 0·01$) were independent predictors of a shorter time-to-progression (TTP) to active WM. Patients with myeloid differentiation factor 88 wild type (*MYD88*^{WT}) genotype ($n = 11$) demonstrated a trend toward shorter TTP [median (95% CI) 1·7 (0·7–8·7) vs. 4·7 (2·4–7·7) years for the *MYD88*^{L265P} cohort, $n = 42$; $P = 0·11$]. The presence of C-X-C chemokine receptor type 4 (*CXCR4*) mutation ($n = 29$) did not impact the TTP (median: 3 years for *CXCR4*^{WT} vs. 5·6 years for *CXCR4*^{MUT}, $P = 0·34$). The overall survival (OS) for patients with SWM (median: 18·1 years) was comparable to an age-, sex- and calendar year-matched USA population (median: 20·3 years, $P = 0·502$). In conclusion, Hb and β_2M at diagnosis represent independent predictors of progression to active WM. Comparable survival of SWM and a matched USA population argues against pre-emptive intervention in this patient population.

Keywords: asymptomatic lymphoplasmacytic lymphoma, IgM monoclonal gammopathy, MYD88, CXCR4.

Disorders associated with monoclonal immunoglobulin M (IgM) exist on a continuous spectrum ranging from monoclonal gammopathy of undetermined significance (MGUS), a precursor condition to Waldenström macroglobulinaemia (WM), an indolent B-cell lymphoma characterised by the presence of circulating IgM monoclonal protein of any size and a lymphoplasmacytic infiltrate involving ≥10% of the bone marrow (BM).[1,2] Besides crossing the 10% threshold of BM infiltration, lymphoplasmacytic cells accumulate genetic aberrations and copy number changes as IgM MGUS clonally evolves to the transitional state of smouldering WM (SWM) and to active WM.[3–5] The 2002 Consensus criteria for initiation of systemic therapy for WM include the presence of constitutional symptoms (recurrent fevers, drenching night sweats, fatigue or significant weight loss), significant cytopenias [haemoglobin (Hb) ≤100 g/l, platelet count ≤100 × 10^9/l], progressive symptomatic organomegaly or complications like symptomatic hyperviscosity attributable to WM.[6–9] Infrequently, the course of WM may be complicated by symptomatic cryoglobulinaemia, symptomatic cold agglutinin disease, histological transformation to an aggressive lymphoma or development of amyloid light-chain (AL) amyloidosis, all of which also require initiation of lymphoplasmacytic lymphoma (LPL) clone-directed systemic therapy.[10–12]

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Approximately one-fifth of the patients with WM can present with SWM, an asymptomatic phase, and are managed with active surveillance alone as early therapeutic intervention in the absence of active disease does not lead to improved survival.[13] However, there can be significant variability in the time-to-progression (TTP) of SWM to symptomatic disease that is dependent on factors such as the levels of Hb, serum β_2-microglobulin (β_2M) and serum IgM.[13,14] However, there are limited data on the impact of the mutational profile of patients with SWM on the time to development of symptomatic disease. To build upon the current knowledge, the objective of our present study was to identify predictors/markers for early progression of SWM to symptomatic disease.

Methods

Patient selection

After Institutional Review Board approval, we included patients with a diagnosis of SWM who were seen at the Mayo Clinic, Rochester, MN between January 1996 and December 2013. SWM was defined by the presence of a circulating IgM monoclonal protein of at least 3g/dl or BM infiltration of at least 10% by LPL cells (irrespective of the size of IgM monoclonal protein) in the absence of any features requiring initiation of WM-directed therapy.[9,15] Patients with IgM MGUS, characterised by circulating monoclonal IgM protein of <3g/dl with <10% marrow LPL infiltrate, were excluded. Prior to the year 2002, the patients who were diagnosed with WM but did not merit initiation of treatment at the time of diagnosis as per the treating haematologist's judgement, were considered to have SWM. The 2002 Consensus criteria were used to guide initiation of therapy for the patients diagnosed after the establishment of these criteria.[9] The cause of death for patients was determined from the medical records for deaths occurring in the hospital. For deaths outside of a hospital setting, correspondence from the next of kin and evaluation through the Rochester Epidemiology Project was utilised to determine the cause. The myeloid differentiation factor 88 (MYD88) and C-X-C chemokine receptor type 4 (CXCR4) testing methodologies are outlined in the Supplement.

Statistical analysis

The primary objective of the study was to evaluate the TTP to symptomatic/active disease, defined as the time from diagnosis of SWM to the initiation of LPL clone-directed therapy, development of AL amyloidosis or transformation to an aggressive lymphoma. The median follow-up was calculated from the date of diagnosis of WM until death or last follow-up. The cumulative incidence of progression to symptomatic disease was calculated using competing risk analysis performed using the method proposed by Gooley *et al.*[16] to account for death as a competing risk for progression of disease. The median values for continuous variables in the present study population were chosen as the cut-offs for dichotomising continuous variables for analysis of TTP (Supplement). To identify the predictors of progression, the baseline characteristics were analysed using Cox proportional hazard method. The factors there were found to be significant on univariable analysis were incorporated into a multivariate Cox regression analysis using the effect likelihood ratio test for identifying independent predictors of progression. The TTP, follow-up and overall survival (OS) were assessed using the Kaplan–Meier method and the log-rank test was used to compare outcomes of (sub)cohorts. The OS of the cohort of patients with SWM was compared to that of the general USA population, matched for age, sex and calendar-year of diagnosis, to assess the degree to which SWM impacts survival. The data for survival for the general USA population was derived from the USA Census tables.

Results

Patient population and baseline characteristics

Between 1996 and 2013, 823 patients with a diagnosis of WM were seen at our centre and of these, 176 (21·5%) with a documented diagnosis of SWM in their records were initially identified as the study population. Of these 176 patients, the degree of marrow LPL infiltrate at the time of initial diagnosis was unavailable in 33 patients who were excluded for further analysis due to our inability to accurately establish the diagnosis of SWM. The baseline characteristics of the 143 patients with an established diagnosis of SWM (the study population are shown in Table I. The

Table I. Baseline characteristics of patients with smouldering Waldenström macroglobulinaemia

Variable	Value
Age in years, median (IQR)	64·3 (59–71)
Sex, % males	62
MYD88^{L265P} mutated, % (n = 53)	79
CXCR4 mutated, % (n = 29)	17
Serum M spike, g/dl	2·0 (1·4–2·5)
Serum IgM, mg/dl	2450 (1610–3570)
Marrow lymphoplasmacytic infiltrate, %	30 (20–50)
Serum viscosity, cp	1·8 (1·4–2·2)
Serum lactate dehydrogenase, u/l	135 (106–162)
Serum IgA, mg/dl	62 (30–123)
Serum IgG, mg/dl	666 (495–990)
Haemoglobin, g/l	123 (112–133)
Platelet count, × 10^9/l	264 (201–338)
β_2M, μg/ml	2·7 (2–3·6)
Serum albumin, g/dl	3·6 (3·3–3·9)

β_2M, β_2-microglobulin; *CXCR4*, C-X-C chemokine receptor type 4; Ig, immunoglobulin; LDH, lactate dehydrogenase; LPL, lymphoplasmacytic lymphoma; *MYD88*, myeloid differentiation factor 88.

median [95% confidence interval (CI)] follow-up of the entire cohort was 9·5 [8·1–11·5] years from diagnosis. Of the 143 patients with SWM, 116 (81%) progressed to require therapy for active WM (113) or AL (three). No patients exhibited histological transformation to a large cell lymphoma prior to development of active disease. Of the 27 patients that did not develop active disease, seven (26%) died due to causes unrelated to WM (competing risk for progression). The median (95% CI) TTP was 4·1 (3·2–5·4) years using Kaplan–Meier analysis. Using competing risk analysis, the cumulative incidence of progression for the entire cohort was a median (95% CI) of 4·3 (3·3–5·4) years. The cumulative incidence of progression was 11% at 1 year, 38% at 3 years, 55% at 5 years and 80% at 10 years (Fig 1). The TTP to active disease was comparable in patients diagnosed before 2003 and subsequently (Supplementary Figure S1). At the time of diagnosis of SWM, seven patients had a Hb level of <100 g/l. Four of these patients had iron deficiency anaemia, two patients had anaemia related to antecedent chronic renal failure (unrelated to AL) and one patient had anaemia of chronic disease attributable to a rheumatological disorder; therefore all these patients were initially observed from the WM standpoint. An additional asymptomatic patient with chronic thrombocytopenia that was stable over many years preceding the diagnosis of SWM (platelet count of 99 $\times$ 10^9/l at initial evaluation, with a Hb level of 126 g/l and normal white blood cell count), remained on active surveillance alone until the last follow-up (5 years from the date of diagnosis of SWM), with a maintained platelet count of 107 $\times$ 10^9/l at last follow-up.

Risk factors for progression

The continuous variables/laboratory parameters were dichotomised using the median value for the cohort (Table I). On univariate Cox proportional hazard analysis, Hb of ≤123 g/l and β_2M ≥2·7 μg/ml were significant predictors of progression (Table II). On a multivariate analysis using Cox regression, these two variables remained independent predictors of progression (Table II). The median (95% CI) TTP for patients with Hb of ≤123 g/l was 3 (2–3·5) years compared to 5·6 (4·6–7·1) years (P = 0·006) for patients with Hb of >123 g/l at diagnosis (Fig 2A). The median (95% CI) TTP for the patients with β_2M ≥2·7 μg/ml was 3·1 (1·8–4·7) years compared to 5·7 (3·7–10·1) years (P = 0·008) for those with β_2M <2·7 μg/ml (Fig 2B). On a multivariate Cox regression analysis, the risk ratios for TTP were comparable for these variables (Table II). Data for both Hb and β_2M at diagnosis was available in 76 patients. The median (95% CI) TTP was 2·4 (1·5–3·1) years for patients with a Hb ≤123 g/l and β_2M ≥2·7 μg/ml (30%, 23/76), 4·1 (2·6–5·4) years for those with either a Hb ≤123 g/l or β_2M ≥2·7 μg/ml (43%, 33/76) and 9·3 (5·6–22·5) years for Hb >123 g/l and β_2M <2·7 μg/ml (n = 20; 26%) at diagnosis (Fig 3). Of 143 patients, *MYD88*^{L265P} mutational status was available in 53 patients. A trend toward shorter TTP for MYD88 wild type (*MYD88*^{WT}) cohort (n = 11) [median (95% CI) 1·7 (0·7–8·7) years compared to the cohort harbouring *MYD88*^{L265P} mutation (n = 42); median 4·7 (2·4–7·7); hazard ratio (HR) 1·73, 95% CI 0·81–3·7; P = 0·11] was observed Figure 4. The *CXCR4* mutation status was available in 29 patients of which five (17%) were *CXCR4* mutated. The median (95% CI) TTP for

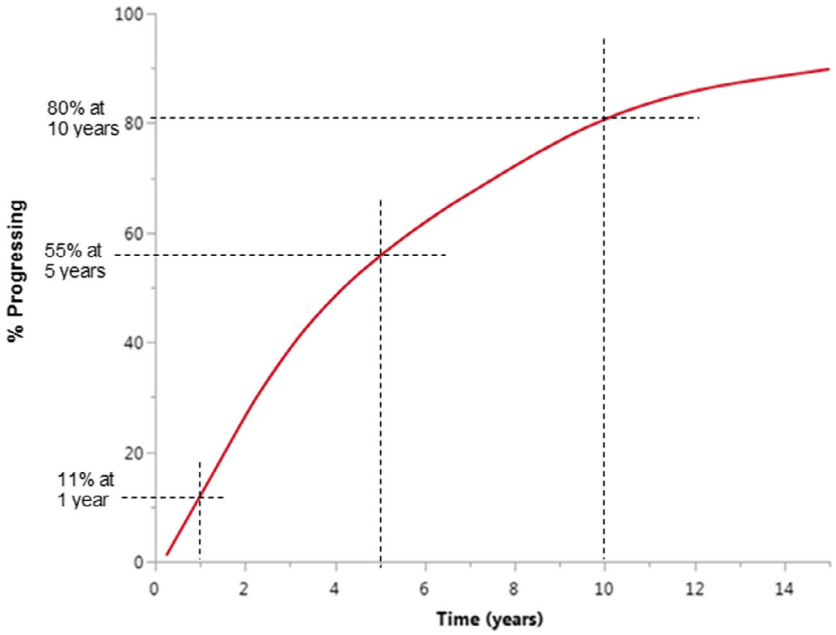


Fig 1. Cumulative incidence of progression for smouldering Waldenström macroglobulinaemia by competing risk analysis. [Colour figure can be viewed at wileyonlinelibrary.com]

Table II. Impact of baseline characteristics on time to progression of smouldering Waldenström macroglobulinaemia

Variable	*N*	*P* value; RR on univariate Cox proportional hazard	*P* value; RR on multivariate Cox regression analysis
Age ≤65 years	143	0·94	
Sex (male/female)	143	0·56	
Marrow infiltration by LPL ≥30%	143	0·97	
Serum IgM ≥2450 mg/dl*	123	0·30	
Haemoglobin ≤123 g/l*	122	0·007; RR 1·75 (95% CI 1·2–2·6)	0·009; RR 2·08 (95% CI 1·2–3·6)
Platelets ≤260 × 10^9/l*	94	0·65	
β_2M ≥2·7 μg/ml*	77	0·009; RR 2·1 (95% CI 1·2–3·6)	0·01; RR 2·0 (95% CI 1·14–3·5)
Serum viscosity ≥1·8 cp	82	0·17	
MYD88^{WT} genotype	53	0·17	
CXCR4^{WT} genotype	29	0·84	
Serum LDH >ULN	60	0·22	
Serum LDH > 135 u/l	60	0·71	
Serum IgA ≤62 mg/dl	71	0·56	
Serum IgG ≤666 mg/dl	70	0·79	
Serum albumin ≤3·6 g/dl	80	0·17	

β_2M, β_2-microglobulin; CI, confidence interval; *CXCR4*^{WT}, C-X-C chemokine receptor type 4 wild type; Ig, immunoglobulin; LDH, lactate dehydrogenase; LPL, lymphoplasmacytic lymphoma; *MYD88*^{WT}, myeloid differentiation factor 88 wild type; RR, risk ratio.
*Median value.

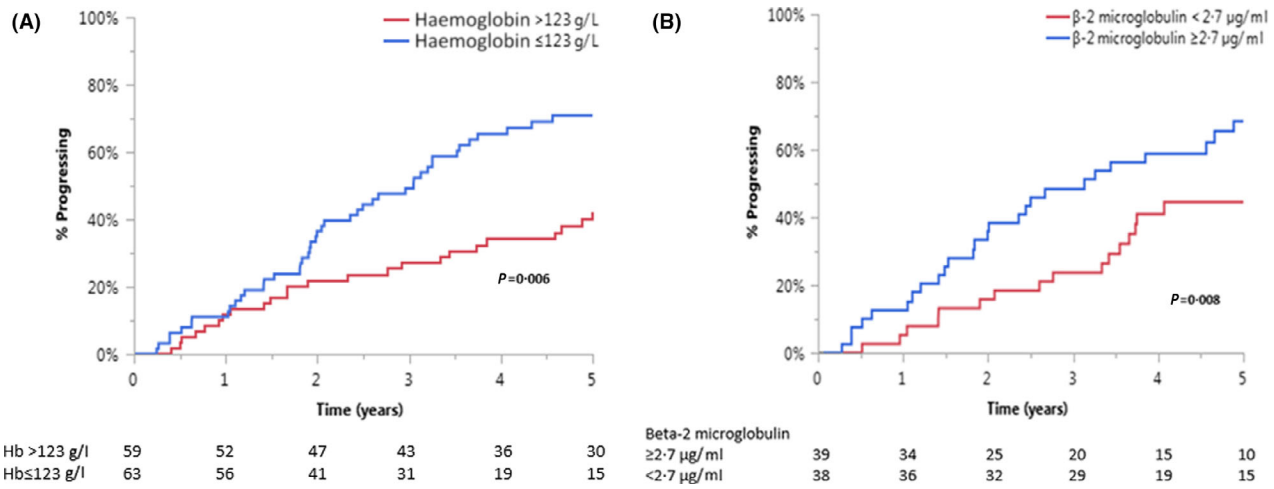
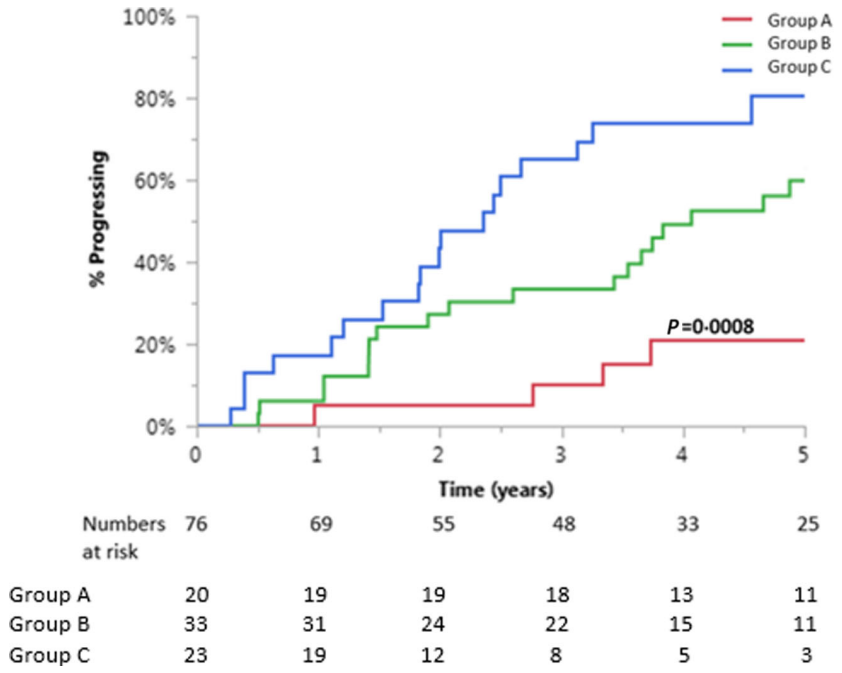


Fig 2. (**A**) Time-to-progression (TTP) for haemoglobin ≤123 *versus* >123 g/l at the diagnosis of smouldering Waldenström macroglobulinaemia. (**B**) TTP for β_2 microglobulin ≥2·7 *versus* <2·7 μg/dl at the diagnosis of smouldering Waldenström macroglobulinaemia. [Colour figure can be viewed at wileyonlinelibrary.com]

CXCR4^{WT} cohort (n = 24) was 3 (2–5·7) years compared to 5·6 (2·8–7·7) years (P = 0·34) for the CXCR4^{MUT} cohort (n = 5), Figure S2.

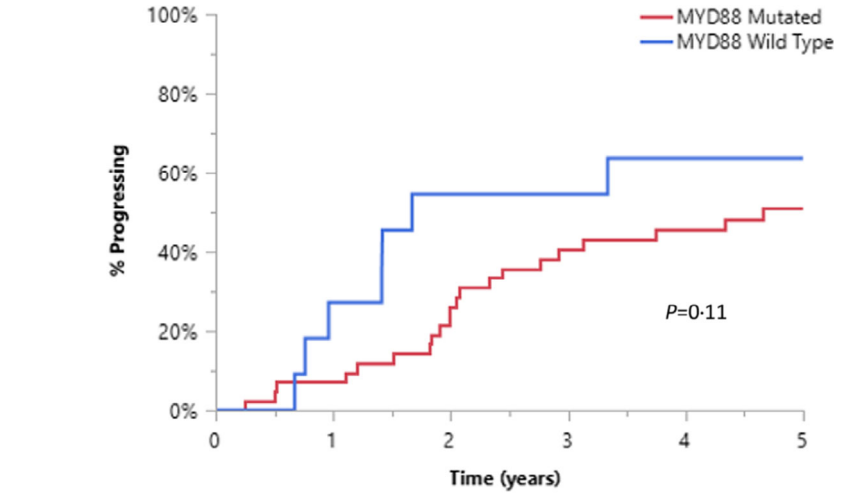
Survival analysis

The median (95% CI) OS from the diagnosis of SWM for the entire cohort was 15·6 (13–20·7) years, with 5- and 10-year survival of 95% and 73%, respectively. A total of 43 (30%) patients had died at the time of last follow-up. Of these, 15 patients died from causes unrelated to WM. Using competing risk analysis, the median (95% CI) OS for the entire cohort was 18·1 (13·4–22·3) years and the 10-year survival rate was 76·5%. For the patients who developed active disease (n = 116), the 5- and 10-year survival rate was 80% and 61%, respectively. The OS for patients with SWM was comparable to an age, sex and calendar-year matched cohort representing the general USA population (median OS 20·3 years, P = 0·502) with a standardised mortality ratio of 1·1 (95% CI 0·8–1·49), (Fig 5).



Numbers at risk	76	69	55	48	33	25
Group A	20	19	19	18	13	11
Group B	33	31	24	22	15	11
Group C	23	19	12	8	5	3

Fig 3. Time-to-progression based on haemoglobin (Hb) and β_2 microglobulin (β_2M) values at diagnosis of Waldenström macroglobulinaemia. Group A represents both Hb >123 g/l and β_2M <2·7 μg/dl; Group B represents either Hb ≤123 g/l or β_2M ≥2·7 μg/dl; Group C represents both Hb ≤123 g/l and β_2M ≥2·7 μg/dl. [Colour figure can be viewed at wileyonlinelibrary.com]



$MYD88^{L265P}$	42	39	31	25	21	17
$MYD88^{WT}$	11	8	5	5	4	4

Fig 4. Time-to-progression based on *MYD88*^{L265P} mutational status of patients with smouldering Waldenström macroglobulinaemia. [Colour figure can be viewed at wileyonlinelibrary.com]

Discussion

The disease course for patients with SWM is remarkably variable. Whereas some patients with SWM can be observed for a prolonged duration, without institution of systemic therapy, there is a subset that requires initiation of systemic therapy within 3 years of diagnosis, similar to the disease course in patients with smouldering multiple myeloma.[13,17] It can be especially anxiety provoking for patients with a diagnosis of malignancy to be considered for observation alone, without a good way to accurately predict the disease progression and requirement for systemic therapy. In the present study, we report the disease characteristics and outcomes of patients with SWM and attempt to identify a cohort of patients with a rapid progression to symptomatic disease. Additionally, we assess the impact of mutational

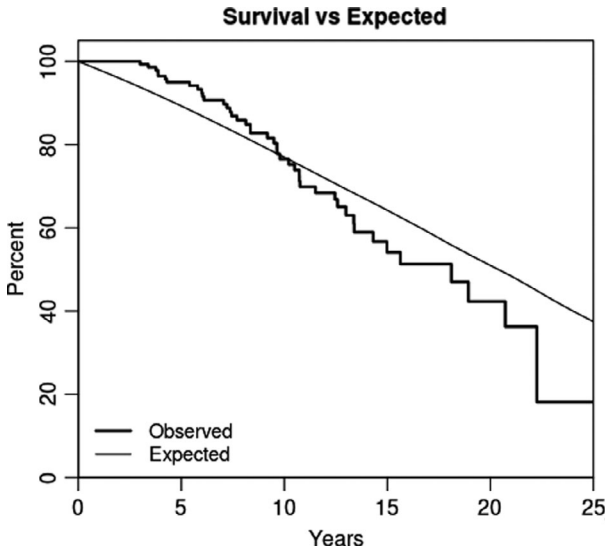


Fig 5. Comparison of observed overall survival of smouldering Waldenström macroglobulinaemia with the expected survival of age- and sex-matched cohort of derived from the general USA population.

status on disease progression in SWM. The study population had a prolonged follow-up, with all patients having a minimum of 3 years of follow-up from diagnosis. We identified low Hb (≤123 g/l) and elevated serum β_2M (≥2·7 μg/ml) as independent predictors of rapid disease progression in this cohort. Using these two variables, we identified a cohort of patients with both low Hb and high β_2M that required treatment initiation within a median time of just over 2 years. These variables were different from those seemingly impacting progression for SWM in a recent multicentre study by Bustoros *et al*.,[18] which could be attributed to different sample sizes as well as the fact that the mentioned study included patients with both SWM and IgM MGUS. We did not include patients with IgM MGUS in our present study and exclusively studied patients with SWM as SWM and IgM can have markedly different outcomes.

The *MYD88*^{WT} mutational status demonstrated a shorter TTP (1·7 years) compared to the *MYD88*^{L265P} mutated cohort (4·7 years), but this observation did not reach statistical significance, likely a reflection of smaller sample size (n = 53). The previously mentioned multicentre study looking at the predictors of disease progression in a cohort with both SWM and IgM MGUS identified *MYD88*^{WT} status as an independent predictor of progression to symptomatic disease in SWM in a subset analysis involving patients from two institutions.[18] Interestingly, the median TTP based on the *MYD88*^{L265P} status in that study was very similar to our present finding. The exact mechanism for rapid progression to active disease in patients with *MYD88*^{WT} is unclear, but on similar lines the *MYD88*^{WT} cohort also experiences a higher risk of histological transformation, implying an underlying genomic instability.[19,20] In the present study, none of the patients with SWM developed histological transformation as the initial criterion for commencing therapy. The impact of the *CXCR4* mutation(s) in SWM is unclear. A previous study reported that patients with SWM with *CXCR4*^{MUT} had a shorter treatment-free interval.[21] This finding was not confirmed in our present cohort, as we could perform only a subset analysis due to the absence of routine *CXCR4* mutation status assessment until recently in our clinical practice. This observation merits further research and external validation. The OS of patients with SWM was noted to be comparable with an age- and sex-matched cohort, supporting our current approach of observation alone with active surveillance at SWM stage.

Our study comes with the limitations of a retrospective design. The 2002 Consensus criteria for treatment initiation in WM were adopted universally at our centre. While the single centre nature of the study meant that the practice patterns were uniform even prior to the establishment of these criteria, the possibility of treating physicians' preference playing a role in the timing of treatment initiation remains. Notably, the time to progression to active WM was comparable in patients diagnosed before the 01/01/2003 and after (Supplementary Figure S1). Our current study findings are limited by the missing data, particularly for β_2M, *MYD88* and *CXCR4* mutation signature. However, this issue is in part unavoidable at present for a study involving patients with SWM, with a prerequisite of protracted follow-up, as both these mutations were identified in WM only recently (*MYD88* mutations in 2012 and *CXCR4* mutations in 2014)[22,23] and most of the patients in the study cohort were diagnosed prior to 2012. The extended follow-up of this cohort with an indolent malignancy is the major strength of the study. The respective median values used for the dichotomisation of the continuous variables ensured uniformity and helped avoid introducing potential biases in our analyses.

In conclusion, our study demonstrates that approximately one-fifth of patients with WM have smouldering disease at the time of diagnosis and almost one-half of the patients do not require treatment initiation for at least 5 years from the time of initial diagnosis. Patients with a low Hb and elevated β_2M at diagnosis have a shorter TTP, and may merit a closer surveillance. Furthermore, the observation of a shorter TTP for patients with SWM with *MYD88*^{WT} genotype validates external data.

Author contributions

Saurabh Zanwar, Jithma P. Abeykoon and Prashant Kapoor designed the study. Saurabh Zanwar, Jithma P. Abeykoon and Prashant Kapoor collected the data. Saurabh Zanwar, Jithma P. Abeykoon, Dirk Larson, Colin Colby and Prashant Kapoor analysed and interpreted the data. Saurabh Zanwar, Jithma P. Abeykoon and Prashant Kapoor wrote the first draft of the manuscript. Saurabh Zanwar, Jithma P.

Abeykoon, Stephen M. Ansell, Morie A. Gertz, Jonas Paludo, Rong He, Rahma Warsame, Patricia T. Greipp, Rebecca L. King, Carrie A. Thompson, Thomas E. Witzig, Martha Q. Lacy, Wilson Gonsalves, Dirk Larson, Colin Colby, Grzegorz S. Nowakowski, David Dingli, Ronald S. Go, Thomas M. Habermann, S. Vincent Rajkumar, Robert A. Kyle, Shaji Kumar and Prashant Kapoor interpreted the data, critically revised the manuscript and all authors approved the final version.

Conflict of interest

None of the authors have any conflict of interest to disclose with regards to this study.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Time-to-progression (TTP) to symptomatic WM based on year of diagnosis. Median TTP in the cohort diagnosed before 2003 was 4.04 years (95% CI: 2.9–5.9 years) compared to 4.06 years (95% CI: 3–5.6 years) for patients diagnosed in 2003 and beyond in the study cohort ($p = 0.8$).

Fig S2. Time-to-progression based on *CXCR4* mutational status of patients with smouldering WM.

Table SI. Comparison of baseline characteristics of cohorts with and without MYD88 genotype testing at diagnosis of Smoldering WM (SWM).

Table SII. Comparison of baseline characteristics of cohorts with and without beta-2 microglobulin testing at diagnosis of Smoldering WM (SWM).

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