bjh commentary

Watch and wait in Waldenström macroglobulinaemia: looking for who to watch carefully and who can wait without worrying. Is it that simple?

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Commentary on Zanwar *et al.* Disease outcomes and biomarkers of progression in smouldering Waldenström macroglobulinaemia. *Br J Haematol.* 2021.

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Waldenström macroglobulinaemia (WM) is a rare indolent B-cell lymphoproliferative disorder affecting older patients and characterised by prolonged survival. WM is considered as an incurable disease, and a high probability of death from WM-unrelated causes, especially from secondary malignancies, has been reported.[1] Only patients with symptomatic disease need immediate therapy. Observation is recommended for patients without immunoglobulin M (IgM)-related complications and/or symptoms related to bone marrow or extramedullary lymphoplasmacytic involvement.[2]

Asymptomatic IgM monoclonal gammopathy encompasses two clinicopathological entities with a distinct risk of progression to symptomatic WM: IgM monoclonal gammopathy of undetermined significance (IgM MGUS) and smouldering WM (SWM). Similarly to several other indolent B-cell lymphomas with heterogeneous disease course managed with initial observation, the challenge for clinical practice remains to identify risk factors for early progression. This is important to inform patients, in terms of follow-up planning and to define high-risk patients who could benefit from early intervention or novel agents. Previous studies in asymptomatic IgM monoclonal gammopathy have reported various variables as potential prognostic marker of progression and various cumulative incidence of progression, summarised in Table I.

In their paper, Zanwar *et al.*[11] focussed on patients with SWM with the aim of identifying risk factors for early progression to symptomatic WM. They evaluated 143 patients with SWM diagnosed between 1996 and 2013 and found that a low haemoglobin level and elevated β_2- microglobulin (β_2M) were associated with shorter time to progression (TTP). This study follows the one by Kyle *et al.*[7] carried out in the same institution from 1974 to 1995 on 48 patients with SWM, with similar rates of progression. In the present study, the authors provide additional information on the prognostic value of β_2M (not evaluated in the previous study due to the few patients with available data) and explore the potential role of myeloid differentiation primary response gene 88 (*MYD88*) and C-X-C motif chemokine receptor 4 (*CXCR4*) mutational status. Interestingly, they were able to identify a subset of patients (30% of patients with the two variables available) with a high risk of progression to symptomatic WM (median TTP 2·4 years). The haemoglobin level, with different thresholds, is one of the variables most often found as predictive of TTP in the studies dealing with asymptomatic IgM monoclonal gammopathy (Table I). It may seem obvious given that the main indication for initiation of treatment in WM is the presence of cytopenias (81% in the present study), mainly anaemia. In the recent study by Bustoros *et al.*[9] the haemoglobin level was also significant for TTP in univariate analysis, but the authors decided not to include it in the prognostic model precisely because its level is used for treatment initiation. β_2M reflects tumour burden. Its prognostic role has already been demonstrated in asymptomatic WM but also in symptomatic WM being part of the International Prognostic Scoring System for Waldenström macroglobulinaemia (IPSSWM) and its revised form.[12,13]

The authors must be commended for the long follow-up (median 9·5 years) of their cohort, with 81% of the patients having progressed at the time of last follow-up. They faced the same difficulties encountered by similar studies on this topic. Given the natural history of the disease, long follow-up is needed. Added to this, the usual retrospective nature of these studies lead to missing data and possible patients lost to follow-up. However, another strength of their study was to restrict it to patients with SWM, knowing the markedly different risk of progression between IgM MGUS and SWM, and to have assembled a relatively large population,

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Table I. Main studies on risk factors for progression in asymptomatic IgM monoclonal gammopathy.

Study	Population	*n*	Risk factors	TTP
Alexanian *et al.*[3]	IgM MGUS	19	Haemoglobin <115 g/l	Median 6·9 years
	SWM	31	β_2M ≥3 mg/l	
			IgM peak >3 g/dl	
Cesana *et al.*[4]	SWM	27	IgM level >3 g/dl	35% at 5 years
			Haemoglobin ≤125 g/l	47% at 10 years
Morra *et al.*[5]	IgM MGUS	138	IgM size	8% at 5 years
	SWM	34	Lymphocytosis	29% at 10 years
Baldini *et al.*[6]	IgM MGUS	217	Haemoglobin	15% at 10 years (MGUS)
	SWM	201	Serum M component	34% at 10 years (SWM)
			Sex	
Kyle *et al.*[7]	SWM	48	BM infiltration	39% at 3 years
			Haemoglobin	59% at 5 years
			Serum M protein	68% at 10 years
			IgA reduction	
Kastritis *et al.*[8]	IgM MGUS	41	BM infiltration ≥50%	3% at 5 years (IgM MGUS)
	SWM	62	Haemoglobin <120 g/l	39% at 5 years (SWM)
Bustoros *et al.*[9]	IgM MGUS + SWM	439	BM infiltration ≥70%	30·8% at 2 years
			IgM level ≥4·5 g/dl	
			β_2M ≥4 mg/l	
			Albumin ≤3·5 g/dl	
Moreno *et al.*[10]	IgM MGUS	64	Immunoparesis	5·2% at 5 years
	SWM	107	BM infiltration ≥20%	

β_2M, β_2-microglobulin; BM, bone marrow; MGUS, monoclonal gammopathy of undetermined significance; SWM, smouldering Waldenström macroglobulinaemia; TTP, time to progression.

considering the rarity of WM. Studies on asymptomatic IgM monoclonal gammopathy are difficult to compare: they often evaluate IgM MGUS and SWM together in different proportions and the same variables are not systematically included in uni- and multivariate analyses. These considerations raise two points of interest.

First, looking at studies on asymptomatic IgM monoclonal gammopathy highlights a controversy over the distinction between WM and IgM MGUS. According to the Mayo Clinic criteria,[14] a bone marrow (BM) lymphoplasmacytic infiltrate of ≥10% with an IgM monoclonal paraprotein of any size is required for WM diagnosis, while the Second Workshop on WM used any level of infiltration of the BM with clonal WM cells.[15] This can largely explain the lack of uniformity between studies in terms of risk factors identified and TTP.

Second, the other question is when to perform a BM biopsy or aspirate when a monoclonal gammopathy is found? Zanwar *et al.*[11] report that patients with SWM represent one-fifth of patients with WM. This proportion is similar to that described by Bustoros *et al.*[9] However, this population of SWM may be underestimated given that about 10–20% of patients with MGUS undergo BM assessment, according to studies from different institutions.[16] In a study by Kastritis *et al.*[8] on 103 patients with asymptomatic IgM monoclonal gammopathy with BM biopsies available, 42% of patients with SWM had IgM paraprotein of <1 g/dl. Based on these data, it would be interesting to perform BM evaluation following any discovery of IgM paraprotein in order to better characterise the diagnosis and better predict the risk of progression to symptomatic WM. Nevertheless, it is not commonly done in routine practice when the IgM level is low without evidence of active disease, particularly in older patients with comorbidities.

MYD88 and *CXCR4* mutations are recurrent somatic mutations in WM. Patients with wild-type *MYD88* WM harbour a higher risk of transformation to aggressive lymphoma and worse survival. *CXCR4* mutations, in particular *CXCR4*^{S338X}, have been associated with higher serum IgM levels, symptomatic hyperviscosity and shorter progression-free survival with ibrutinib.[17] Testing for *MYD88* and *CXCR4* mutations is increasingly used in WM but their discovery is <10 years old. Consequently, few data are available on their prognostic value for TTP in SWM. In the study by Bustoros *et al.*[9] (with both IgM MGUS and SWM), *MYD88* mutation status could not be included in the prognostic model but by combining their cohort with the Greek cohort, they demonstrated that patients with *MYD88* wild-type disease had a significantly shorter TTP. The present study is consistent with these data, with very similar TTP based on the *MYD88* mutational status. Statistical significance was not reached probably due to lack of power. Concerning *CXCR4* mutations, no difference was found in terms of TTP but the *CXCR4* mutational status was known for only one-fifth of the cohort, precluding any conclusion. These molecular

markers and their potential role in predicting TTP should ideally be analysed in a prospective study with standardised testing.

In summary, the data presented by Zanwar *et al.*[11] provide a useful tool to identify patients with SWM at higher risk of progression with two variables easily available in routine practice. Their data would need validation in an external cohort of patients with SWM. The last point of interest presented by the authors is the long overall survival of patients with SWM, comparable to a matched cohort representing the USA population, highlighting the need to accurately identify patients with SWM at very high risk of progression. This study illustrates an interesting but difficult field of research, given all the issues discussed above. Finally, to bring even more difficulties, we must keep in mind that some patients with SWM can experience mild symptoms, not enough to initiate treatment but enough to alter quality of life.[18] Further studies on SWM should report quality of life outcomes.

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