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Long survival in patients with Waldenström macroglobulinaemia diagnosed at a young age

Waldenström Macroglobulinaemia (WM) is an IgM-secreting lymphoplasmacytic lymphoma, with median age at diagnosis of 69 years and median overall survival (OS) approximating 10 years (Castillo *et al*, 2015). Recurrent mutations in *MYD88* and *CXCR4* have been identified in 95% and 40% of patients, respectively (Treon *et al*, 2012; Hunter *et al*, 2014). As patients younger than 50 years old make up less than 10% of all cases (Castillo *et al*, 2015), there exists a dearth of data on young WM patients. This study aimed to analyse the characteristics, response and survival outcomes of young WM patients.

A retrospective study was conducted on consecutive patients diagnosed with WM at age 45 years or younger, who were evaluated at our institution. Patients were diagnosed between January 1983 and December 2017. Pertinent clinical data were gathered at diagnosis and prior to primary therapy. We also gathered indications to treat, treatment received and response to therapy. Diagnosis and treatment indications were based on the 2nd International Workshop for WM (IWWM) criteria (Kyle *et al*, 2003; Owen *et al*, 2003). Response was assessed using the 6th IWWM criteria (Owen *et al*, 2013). *MYD88* and *CXCR4* mutational status was evaluated as previously described (Treon *et al*, 2012; Hunter *et al*, 2014). Time to events were estimated using the Kaplan–Meier method, and comparisons made using the log-rank test. Calculations and graphs were obtained using STATA/SE 13.1.

The clinical characteristics of the 124 patients who met our inclusion criteria are shown in Table I. The *MYD88* L265P mutation was identified in 38 of 42 patients (90%) tested, and *CXCR4* mutations in 16 of 36 patients (44%) tested; 8 were frameshift and 8 were nonsense mutations. Nineteen patients (15%) have not yet been treated for WM, 43 patients (35%) needed therapy at the time of diagnosis, and for the remaining 62 patients, the median time to treatment initiation was 2·5 years (95% confidence interval [CI] 0·8–5·6 years). In the 19 patients that have not yet received treatment, the median follow-up time is 5 years (range 0·1–31·2 years). Among 105 patients who have received WM-directed therapy, indications for treatment included symptomatic hyperviscosity (n = 43; 41%), extramedullary disease (n = 35; 33%), constitutional symptoms (n = 35; 33%), anaemia (n = 20; 19%) and peripheral neuropathy (n = 20; 19%). As primary therapy, 29 patients (28%) received nucleoside analogue-based, 30 (29%) alkylator-based and 18 (17%) proteasome inhibitor-based therapy, 22 (21%) anti-CD20 monoclonal antibody, 2 (2%) BTK inhibitors and 4 (4%) other therapies. Overall response rate (ORR) was 83%, with complete (CR)/very good partial response (VGPR) rate of 14%, and partial (PR)/minor response (MR) rate of 69%. The 61 patients who received rituximab in combination with nucleoside analogues, alkylators or proteasome inhibitors had higher CR/VGPR rate (17% vs. 9%, respectively) and higher PR/MR rate (71% vs. 64%, respectively) than the 21 patients who received rituximab alone (P = 0·02). The median progression-free survival (PFS) after primary therapy was 2·4 years (95% CI 1·7–3·9 years; Fig 1A). The median PFS after primary therapy was longer in patients who received rituximab in combination than in patients who received rituximab alone (3·9 years, 95% CI 2·0–11·7 years vs. 1·4 years, 95% CI 0·8–3·8 years; log-rank P = 0·03; Fig 1B). Median follow-up for all patients was 7·8 years and median OS was not reached. The 5-year and 10-year OS rates were 98% (95% CI 93–99·5%) and 86% (95% CI 75–93%), respectively (Fig 1C). The median survival after primary therapy was 25·0 years (95% CI 20·0–not reached; Fig 1D). No difference in survival after primary therapy was observed between patients treated with rituximab combinations and rituximab alone (log-rank P = 0·55), or between patients who responded or not to primary therapy (log-rank P = 0·32), although the sample size was small.

Our study shows that a third of young patients with WM need therapy at diagnosis, 40% of patients need therapy due to symptomatic hyperviscosity, and the 10-year OS rate was 86%. Other notable findings include deeper responses and longer PFS in young WM patients treated with combination regimens when compared to rituximab alone.

The rate of symptomatic hyperviscosity as a criterion to treat young WM patients appears higher than in the general WM population. This is a novel finding that has important implications in the care of young patients with WM. The reasons behind the high rates of symptomatic hyperviscosity

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Table I. Clinical characteristics at diagnosis and at primary therapy initiation of 124 Waldenström macroglobulinaemia patients diagnosed at age 45 years or younger.

Characteristic	At diagnosis Median (range)	At primary therapy Median (range)
Age, years	42 (29–45)	43 (29–63)
Haemoglobin, g/l	117 (40–151)	105 (40–143)
Platelet count, $\times 10^9$/l	246·5 (31–526)	235 (31–526)
Serum IgM, g/l	35·7 (3·98–110)	46·56 (4·6–110)
Beta-2-microglobulin, mg/l	2·2 (0·9–21·7)	2·6 (0·9–21·7)
Bone marrow involvement, %	50 (2–100)	60 (2–100)

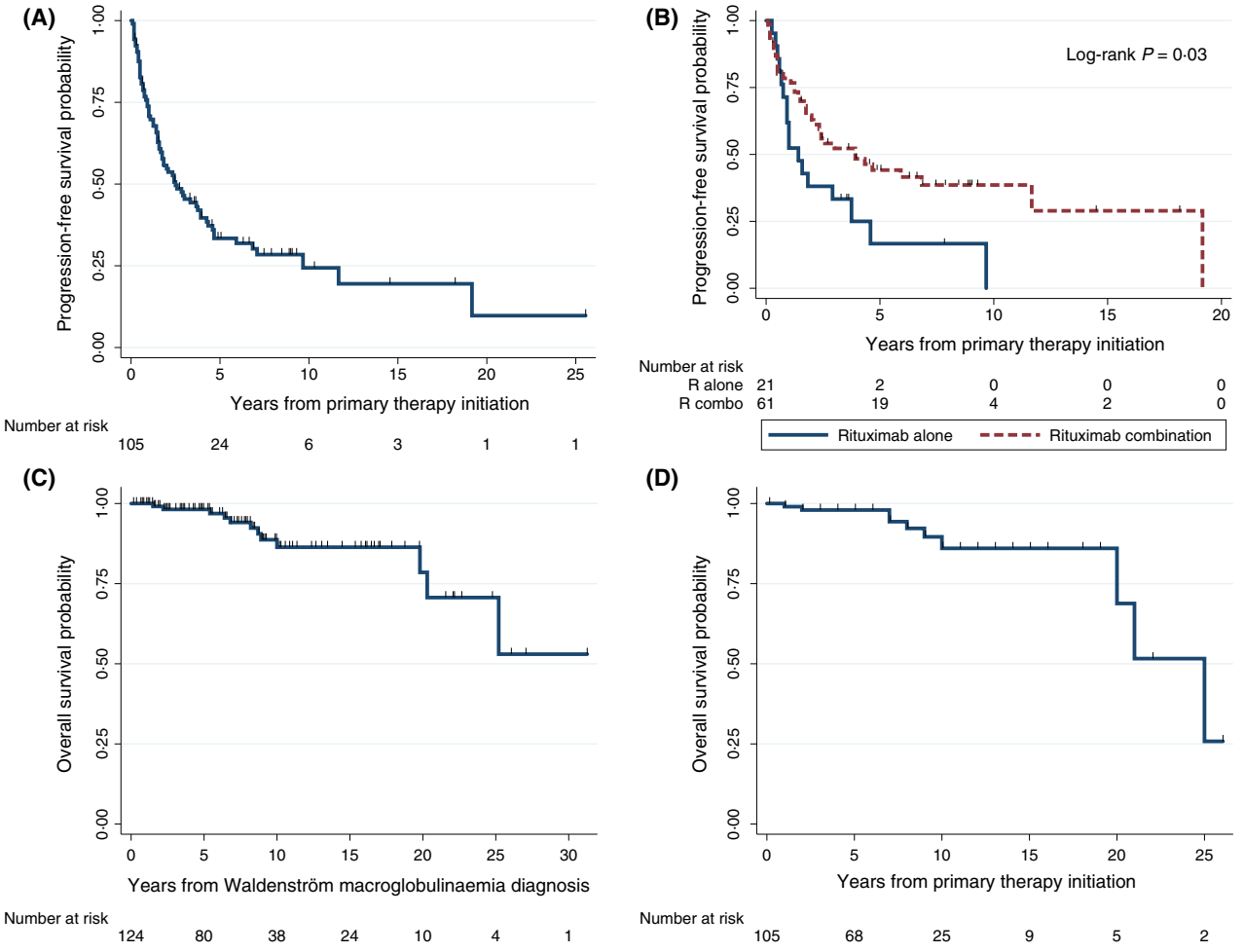

Fig 1. Progression-free survival (PFS) estimate from (A) primary therapy initiation and (B) rituximab-containing primary therapy initiation. Overall survival (OS) estimate from (C) diagnosis and (D) primary therapy initiation in 124 patients with Waldenström macroglobulinaemia diagnosed at age 45 years or younger. R, rituximab. [Colour figure can be viewed at wileyonlinelibrary.com]

in young WM patients are unclear. *CXCR4* mutations have been associated with higher rates of symptomatic hyperviscosity, which could partly explain our findings (Gustine *et al*, 2017). Approximately, one-third of patients needed therapy at the time of diagnosis and half of the patients needed therapy within 1 year from diagnosis. This finding is similar to the observations from a population-based study in WM patients aged 65 or older (Olszewski *et al*, 2016). Our study suggests encouraging OS rates in young WM patients. The 10-year OS rate (86%) appears somewhat higher than the rate reported in a Surveillance, Epidemiology and End Results-based study between 2001 and 2010, in which WM patients aged 50 years or younger had a 10-year OS rate of 75% (Castillo *et al*, 2015). We believe this information would

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be of help for healthcare practitioners during prognostic discussions with young WM patients. Our study also shows that rituximab combination regimens are associated with deeper responses and longer PFS than rituximab alone in young WM patients. There are scant data comparing outcomes between patients treated with rituximab alone or in combination. The recently published INNOVATE study showed deeper responses and higher 30-month PFS rates with the combination of ibrutinib and rituximab versus placebo and rituximab (Dimopoulos *et al*, 2018). However, in this large randomized study, no OS difference could be detected between the groups. With a 10-year OS rate of 86% in young WM patients, one could argue that OS might not be an optimal outcome of interest in these patients. Not surprisingly, OS benefits have not been apparent with any intervention in population-based or randomized studies (Olszewski *et al*, 2017; Dimopoulos *et al*, 2018). Despite the limitations of this study (i.e. retrospective, heterogeneous therapies, missing data and incomplete follow-up), we believe our findings provide a positive perspective on the outcomes of WM patients diagnosed at a young age.

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Authorship contribution

AB and JJC designed the study and performed the analysis. AB and JNG gathered the data. LX, GY and ZRH performed molecular testing in patients' samples. JJC, JG, KM, TED and SPT took care of patients. AB and JJC drafted the manuscript. All the authors critically reviewed and approved the final manuscript.

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Comment on: type 1 cryoglobulinaemia leading to gangrene of the toes and ischaemic ulceration

Thanks to Siow *et al* (2018) for sharing their experience of diagnosing and managing type 1 cryoglobulinaemia.

I just wish to clarify what radiological imaging was undertaken, given that type 1 cryoglobulinaemia results from monoclonal expansion of B cells?

Whilst it is stated the patient 'did not fulfil the diagnostic criteria for multiple myeloma', presence of osteosclerotic lesions (as we have also encountered in a patient presenting with type 1 cryoglobulinaemia and a normal bone marrow aspirate), or, one supposes, a solitary plasmacytoma or indeed any lymphadenopathy, would change the patient's management.

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Siow, W., Chana, J., Pawson, R., Riat, R., Pushkaran, B. & Aitchison, R. (2018) Type 1 cryoglobulinaemia leading to gangrene of the toes and ischaemic ulceration. *British Journal of Haematology*, **181**, 724–724.

Comment on: Type 1 cryoglobulinaemia leading to gangrene of the toes and ischaemic ulceration

I read with great interest the recent article by Siow *et al* (2018) regarding type 1 cryoglobulinaemia leading to gangrene of the toes and ischaemic ulceration. I would like to add some points.

Type 1 cryoglobulinaemia is usually asymptomatic, but when symptomatic it is associated with findings of hyper viscosity and vascular occlusions due to immunoglobulins, which precipitate in the generally colder body regions. Reynaud phenomenon, livedo reticularis and digital ischemia can develop. Usually, type 1 cryoglobulinaemia is associated with multiple myeloma, Waldenström macroglobulinaemia, chronic lymphocytic leukaemia and monoclonal gammopathy of unknown significance (den Hollander & Swaak, 2002).

Sometimes the first finding of underlying disease may be type 1 cryptoglobulinaemia-related symptoms and findings. Therefore, the patient's primary disease will be missed and the diagnosis will be delayed because there are no additional symptoms or findings associated with the underlying disease. If type 1 cryoglobulinaemia is not included in the preliminary diagnosis and not investigated as recommended (Ferri *et al*, 2002), it can easily be overlooked. At this point, these patients are followed up for incorrect diagnoses, such as connective tissue diseases, vasculitis and Buerger disease, with delays in effective treatments and increased morbidity. For this reason, dermatologists, rheumatologists, haematologists and cardiovascular surgeons should be alert for similar cases and made aware of the significance of this disorder.

I hope that the above-mentioned items might add to the value of the well-written article by Siow *et al* (2018).

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