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 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 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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>At diagnosis</th>
<th>At primary therapy</th>
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<tbody>
<tr>
<td></td>
<td>Median (range)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Age, years</td>
<td>42 (29–45)</td>
<td>43 (29–63)</td>
</tr>
<tr>
<td>Haemoglobin, g/l</td>
<td>117 (40–151)</td>
<td>105 (40–143)</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/l</td>
<td>246·5 (31–526)</td>
<td>235 (31–526)</td>
</tr>
<tr>
<td>Serum IgM, g/l</td>
<td>35·7 (3·98–110)</td>
<td>46·56 (4·6–110)</td>
</tr>
<tr>
<td>Beta-2-microglobulin, mg/l</td>
<td>2·2 (0·9–21·7)</td>
<td>2·6 (0·9–21·7)</td>
</tr>
<tr>
<td>Bone marrow involvement, %</td>
<td>50 (2–100)</td>
<td>60 (2–100)</td>
</tr>
</tbody>
</table>

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]
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.

Disclosures

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