Serum IgM level as predictor of symptomatic hyperviscosity in patients with Waldenström macroglobulinaemia

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Received 21 January 2017; accepted for publication 6 March 2017

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Summary

Symptomatic hyperviscosity is a common clinical manifestation in patients with Waldenström macroglobulinemia (WM) and high serum IgM levels. Prompt intervention is required to prevent catastrophic events, such as retinal or central nervous system bleeding. Identifying patients at high risk of symptomatic hyperviscosity might support the decision to treat asymptomatic patients before irreversible damage occurs. We carried out a large retrospective study in 825 newly diagnosed WM patients, of who 113 (14%) developed symptomatic hyperviscosity. The median serum IgM level at the time of symptomatic hyperviscosity was 61.8 g/l (range 31–124 g/l). Forty-four patients (36%) had symptomatic hyperviscosity at the time of WM diagnosis. A serum IgM level >60 g/l at diagnosis was associated with a median time to symptomatic hyperviscosity of 3 months, whereas the median time for patients with serum IgM level of 50–60 g/l was approximately 3 years. Adjusting for other clinical factors, the odds of developing symptomatic hyperviscosity were 370-fold higher with serum IgM levels >60 g/l, and showed an association with CXCR4 mutational status. Symptomatic hyperviscosity did not impact overall survival (P = 0.12). The findings support the use of serum IgM level >60 g/l as a criterion for initiation of therapy in an otherwise asymptomatic WM patient.

Keywords: Waldenström macroglobulinaemia, hyperviscosity, immunoglobulin M, MYD88 mutation, CXCR4 mutation.

Hyperviscosity syndrome is a common clinical manifestation of Waldenström macroglobulinemia (WM), a malignant B-cell lymphoma characterized by the excessive secretion of monoclonal IgM (Owen et al., 2003). Accumulation of excess IgM in the bloodstream increases serum viscosity and may cause symptomatic hyperviscosity in up to 30% of patients with WM (Mehta & Singhal, 2003). Spontaneous epistaxis, new-onset headaches and visual disturbances often define the clinical presentation of hyperviscosity syndrome (Stone & Bogen, 2012). Prompt intervention is required to prevent catastrophic events such as central nervous system or retinal bleeding (Castillo et al., 2016).

Current consensus guidelines recommend the initiation of WM-directed therapy only for patients with symptomatic hyperviscosity, rather than when a specified serum IgM level is reached (Kyle et al., 2003). Individual patients can develop hyperviscosity-related symptoms at different serum IgM levels (‘symptomatic threshold’) (Fahey et al., 1965), and there are currently no data to justify early initiation of treatment for asymptomatic patients with WM. However, asymptomatic patients with an elevated serum IgM level are often treated to pre-empt the development of symptomatic hyperviscosity. Given the risk of hyperviscosity-related injury, empiric treatment of high serum IgM levels irrespective of symptomatic status has been proposed as a reasonable criterion for treatment initiation in patients with WM (Treon, 2015).

We therefore set out as part of this retrospective study to determine the serum IgM threshold at which the risk of symptomatic hyperviscosity would outweigh continued observation and support the decision to initiate WM-directed therapy.

Methods

Cohort selection and variable identification

We performed a retrospective review of patients with a clinicopathological diagnosis of WM (Owen et al., 2003) who were seen in our WM clinic between 1 January 1999 and 31
May 2016. Patients who were untreated at the time of presentation were included in this study. Medical files were manually reviewed to identify cases of symptomatic hyperviscosity between the time of WM diagnosis and initiation of frontline therapy. Symptomatic hyperviscosity was defined by the presence of recurrent epistaxis, new-onset headaches, new-onset blurry vision, slowed mentation, and/or presence of retinal vessel engorgement, tortuosity, sausaging, and/or retinal haemorrhages that were attributed to WM. Pertinent clinical and pathological data were gathered. The presence of MYD88 and CXCR4 mutations were detected by allele-specific polymerase chain reaction (AS-PCR) and Sanger sequencing methods, respectively, as previously described (Xu et al., 2013, 2015).

Statistical analysis

Continuous variables were categorized to facilitate analysis. Univariate and multivariate logistic regression models were fit to evaluate the association between clinical variables and the risk of symptomatic hyperviscosity; the outcome measure was odds ratio (OR) with 95% confidence interval (CI). The time from WM diagnosis to development of symptomatic hyperviscosity was defined as the time in months between WM diagnosis and identification of symptomatic hyperviscosity. Patients with symptomatic hyperviscosity at initial presentation (i.e. within 30 days of WM diagnosis) were excluded from this analysis. The survival from WM diagnosis was defined as the time in months between WM diagnosis and last follow-up or death. Time to events was estimated using the Kaplan–Meier method and comparisons between groups were made using the log-rank test. The Cox proportional-hazard regression method was used to fit univariate and multivariate models for overall survival; the outcome measure was hazard ratio (HR) with 95% CI. For both the regression and survival univariate models, only the variables with a P-value <0.05 were included in the multivariate analysis. P-values were two-sided and considered statistically significant if <0.05. All calculations and graphs were obtained using STATA/SE 13.1 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

A total of 113 patients (14%) who developed symptomatic hyperviscosity were identified in a cohort of 825 treatment-naive patients with WM. The epoch of WM diagnosis included: 1991–2000 (n = 49; 6%), 2001–2005 (n = 178; 22%), 2006–2010 (n = 310; 38%) and 2011–2016 (n = 288; 35%). The clinical characteristics of these patients at time of WM diagnosis are shown in Table I. WM patients who developed symptomatic hyperviscosity were more likely to have a haemoglobin level ≤115 g/l (57% vs. 31%), bone marrow involvement ≥50% (42% vs. 29%) and be younger than 65 years (78% vs. 59%) compared to patients who did not develop symptomatic hyperviscosity. WM patients who developed hyperviscosity were more likely to have serum IgM levels >30 g/l. No difference in the proportion of patients who had detectable cryoglobulins was observed between patients with and without symptomatic hyperviscosity (P = 0.67). The clinical presentation of symptomatic hyperviscosity included: blurry vision, retinal vessel sausaging, and/or retinal haemorrhages (n = 97; 86%), epistaxis (n = 85; 75%), headaches (n = 42; 37%) and slowed mentation (n = 12; 11%).

Risk of symptomatic hyperviscosity

The median serum IgM level at the time of symptomatic hyperviscosity was 61.8 g/l (range 31–124 g/l). The cumulative incidence of symptomatic hyperviscosity at 12, 24, 36, 48, 60 and 120 months from WM diagnosis was 10.8%, 14.7%, 16.8%, 17.6%, 18.2% and 26.0%, respectively (Fig 1A). No cases of symptomatic hyperviscosity were identified in patients with a serum IgM level <30 g/l (n = 431). Forty-one patients (36%) had symptomatic hyperviscosity at the time of initial presentation with WM. After excluding these patients, the median time from WM diagnosis to hyperviscosity was 3 months for patients with serum IgM level >60 g/l at diagnosis. The median time to hyperviscosity for patients with serum IgM levels 50–60, 40–50 and 30–40 g/l was 36, 32 and 156 months, respectively. The median time to hyperviscosity for patients with serum IgM levels of 30 g/l or lower was not reached (log-rank P < 0.001; Fig 1B).

The crude incidence of symptomatic hyperviscosity in patients with serum IgM levels ranging between 30–40, 40–50, 50–60 and >60 g/l was 3% (n = 3/120), 22% (n = 21/95), 32% (n = 28/88) and 67% (n = 61/91), respectively (P < 0.001; Fig 2A). The risk of symptomatic hyperviscosity increased exponentially with each increasing category of serum IgM level (R² = 0.98).

By univariate analysis, the odds of symptomatic hyperviscosity were significantly higher with a haemoglobin level ≤115 g/l and bone marrow involvement ≥50% at the time of WM diagnosis, and with serum IgM levels >30 g/l. Age >65 years at WM diagnosis was associated with lower odds of hyperviscosity. Sex, platelet count, serum β₂-microglobulin, cryoglobulins, or cold agglutinins were not associated with higher or lower odds of symptomatic hyperviscosity. In the multivariate analysis, serum IgM levels 30–40, 40–50, 50–60 and >60 g/l were independently associated with 20-, 50-, 40- and 370-fold higher odds of symptomatic hyperviscosity. Age >65 years at WM diagnosis (OR 0.45, 95% CI 0.24–0.81; P = 0.007) also remained associated with lower odds of symptomatic hyperviscosity. The univariate and multivariate models are shown in Table II.
Management of patients with symptomatic hyperviscosity

Seventy-seven patients (68%) received emergent plasmapheresis for symptomatic hyperviscosity; 28 patients (36%) underwent plasmapheresis at our institution. The median serum IgM level before plasmapheresis was 63 g/l (IQR 54–67 g/l). Our protocol is to perform three sessions of plasmapheresis in 1 week followed by weekly plasmapheresis until WM-directed therapy takes effect, serum IgM level drops below 60 g/l, and the patient is free from hyperviscosity symptoms. Data on serum IgM levels during plasmapheresis were available in 53 patients (69%). The median serum IgM levels were 51 g/l (IQR 45–72 g/l), 38 g/l (IQR 28–46 g/l) and 25 g/l (IQR 21–32 g/l), respectively (Fig 2B).

WM-directed therapy was initiated for all but one patient in response to developing symptomatic hyperviscosity; one patient refused treatment. Combination therapy with an anti-CD20 monoclonal antibody and a proteasome inhibitor (n = 71; 63%), alkylator (n = 13; 12%), nucleoside analogue (n = 12; 11%), or immunomodulator (n = 7; 6%) was initiated for most patients. Ibrutinib (n = 5; 4%), everolimus (n = 2; 2%), and rituximab alone (n = 2; 2%) were also utilized. Resolution of hyperviscosity-related symptoms was observed for all patients who received intervention.

Survival analysis

With a median follow-up of 54 months (95% CI 51–60 months), 78 patients (10%) have died. No difference in overall survival was observed between patients with and without symptomatic hyperviscosity (Fig 3; P = 0.12). By univariate analysis, the risk of death significantly increased with age >65 years and serum β2-microglobulin >3.0 mg/l at the time of WM diagnosis. Sex, haemoglobin level, platelet count, bone marrow involvement and serum IgM levels at the time of WM diagnosis, as well as presence of cryoglobulins or cold agglutinins, were not associated with risk of death. In the multivariate model, age >65 years (HR 2.46, 95% CI 1.56–3.88; P < 0.001) and serum β2-microglobulin >3.0 mg/l (HR 1.74, 95% CI 1.11–2.73; P = 0.02) at WM diagnosis were independent risk factors for mortality.
diagnosis were independently associated with an adverse prognosis. The univariate and multivariate models are shown in Table III.

Impact of tumour genotype

Tumour genotyping was performed in 224 patients. Among these patients, 216 (96%) carried the MYD88 L265P mutation and 8 (4%) were wild-type for MYD88. Of the MYD88 mutated patients, 106 (47%) carried at least one CXCR4 mutation; 64 (60%) had a nonsense mutation, 37 (35%) had a frameshift mutation and 5 (5%) had both a nonsense and frameshift mutation. Patients who developed symptomatic hyperviscosity had a similar rate of mutated MYD88 (100% vs. 96%; \( P = 0.21 \)) versus patients who did not develop symptomatic hyperviscosity. None of the patients with wild-type MYD88 developed symptomatic hyperviscosity. Patients who developed symptomatic hyperviscosity were more likely to carry a CXCR4 mutation (78% vs. 42%; \( P < 0.001 \)) versus those who did not develop symptomatic hyperviscosity. For CXCR4 mutated patients, the odds of presenting with symptomatic hyperviscosity were higher versus wild-type CXCR4 patients (OR 4.94, 95% CI 2.14–11.4; \( P < 0.001 \)). Moreover, symptomatic hyperviscosity was more likely with a CXCR4 nonsense mutation than frameshift mutation (41% vs. 5%; \( P < 0.001 \)). Patients with a CXCR4 nonsense mutation had
higher odds of symptomatic hyperviscosity (OR 9.41, 95% CI 2.93–22.49; P < 0.001) than patients with a CXCR4 frameshift mutation (OR 0.79, 95% CI 0.16–3.87; P = 0.77).

In an exploratory analysis, we evaluated the presence of CXCR4 mutations against haemoglobin and serum IgM levels in a multivariate model (n = 224). In this model, CXCR4 mutations remained associated with higher odds (OR 3.60, 95% CI 1.42–9.41; P = 0.001) of developing symptomatic hyperviscosity. Serum IgM levels >30 g/l (OR 4.07, 95% CI 1.14–13.51; P = 0.04) and >60 g/l (OR 2.69, 95% CI 1.23–5.84; P = 0.01) were also associated with higher odds of symptomatic hyperviscosity. Haemoglobin level was not associated with higher or lower odds of symptomatic hyperviscosity (P = 0.89).

**Discussion**

Symptomatic hyperviscosity may herald catastrophic events, such as central nervous system or retinal bleeding (Castillo et al, 2016). To prevent hyperviscosity-related injury, empiric treatment at high serum IgM levels has been proposed as a reasonable treatment criterion for patients with WM regardless of symptomatic status (Treon, 2015). However, a paucity of published data exists to suggest the serum IgM level for which the risk of symptomatic hyperviscosity would support initiation of WM-directed therapy. Current consensus criteria also do not address the role of treatment in asymptomatic WM patients with high serum IgM levels (Kyle et al, 2003). This prompted us to investigate the risk of symptomatic hyperviscosity in 825 treatment-naive patients with WM to identify the serum IgM level at which treatment initiation could be reasonably considered.

**Table II.** Univariate and multivariate models for symptomatic hyperviscosity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
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<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>0.42 (0.26–0.66)</td>
<td>&lt;0.001</td>
<td>0.45 (0.24–0.81)</td>
<td>0.007</td>
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<tr>
<td>Male sex</td>
<td>1.07 (0.71–1.60)</td>
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<tr>
<td>Haemoglobin level ≤115 g/l</td>
<td>2.86 (1.91–4.29)</td>
<td>&lt;0.001</td>
<td>1.13 (0.66–1.96)</td>
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<tr>
<td>Platelet count ≤100 × 10^9/l</td>
<td>1.69 (0.62–4.62)</td>
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<tr>
<td>Serum β_2-microglobulin &gt;3–6 mg/l</td>
<td>1.33 (0.90–1.98)</td>
<td>0.16</td>
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<tr>
<td>Cold agglutinins</td>
<td>1.39 (0.71–2.72)</td>
<td>0.34</td>
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<tr>
<td>Cryoglobulins</td>
<td>1.16 (0.58–2.32)</td>
<td>0.68</td>
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<tr>
<td>Bone marrow involvement ≥50%</td>
<td>1.84 (1.22–2.76)</td>
<td>0.003</td>
<td>0.95 (0.55–1.64)</td>
<td>0.84</td>
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<tr>
<td>Serum IgM level 0–10 g/l</td>
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<td></td>
<td>Reference</td>
<td></td>
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<tr>
<td>Serum IgM level 10–20 g/l</td>
<td>1.86 (0.34–10.3)</td>
<td>0.48</td>
<td>1.78 (0.32–9.88)</td>
<td>0.508</td>
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<tr>
<td>Serum IgM level 20–30 g/l</td>
<td>4.11 (0.84–20.1)</td>
<td>0.08</td>
<td>4.05 (0.83–19.9)</td>
<td>0.08</td>
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<tr>
<td>Serum IgM level 30–40 g/l</td>
<td>22.7 (5.25–98.2)</td>
<td>&lt;0.001</td>
<td>20.6 (4.73–89.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum IgM level 40–50 g/l</td>
<td>51.2 (11.7–224.4)</td>
<td>&lt;0.001</td>
<td>49.1 (11.0–219.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum IgM level 50–60 g/l</td>
<td>50.8 (11.0–234.9)</td>
<td>&lt;0.001</td>
<td>44.0 (9.35–206.6)</td>
<td>&lt;0.001</td>
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<tr>
<td>Serum IgM level &gt;60 g/l</td>
<td>387.2 (70.8–2116.7)</td>
<td>&lt;0.001</td>
<td>372.1 (65.2–2121.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval. Age, sex, haemoglobin level, platelet count, and serum β_2-microglobulin level are at the time of Waldenström macroglobulinaemia diagnosis.

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*British Journal of Haematology, 2017, 177, 717–725*
As part of these efforts, the cumulative incidence and timing of symptomatic hyperviscosity were examined. One in ten patients with WM develops symptomatic hyperviscosity within 1 year of WM diagnosis, and the risk continues to increase over time with a 10-year incidence of 26%. Symptomatic hyperviscosity has been previously reported in up to 30% of WM patients (Mehta & Singhal, 2003). Additionally, a shorter elapsed time to the development of symptomatic hyperviscosity was observed for patients with a high serum IgM level at the time of WM diagnosis. Patients with a serum IgM level >60 g/l have a particularly acute risk of symptomatic hyperviscosity, occurring in more than half these patients within a few months of diagnosis. These results may be relevant to identify patients for whom increased monitoring is clinically indicated.

A serum IgM level of at least 30 g/l was identified as the threshold at which patients with WM are at risk for developing symptomatic hyperviscosity. Prior reports have described the occurrence of symptomatic hyperviscosity when the serum viscosity is >4.0 centipoise (Crawford et al, 1985; Table III. Univariate and multivariate models for overall survival.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>2.55 (1.62–4.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.58 (0.97–2.58)</td>
<td>0.06</td>
</tr>
<tr>
<td>Haemoglobin level ≤115 g/l</td>
<td>1.14 (0.71–1.84)</td>
<td>0.60</td>
</tr>
<tr>
<td>Platelet count ≤100 × 10⁹/l</td>
<td>0.88 (0.22–3.59)</td>
<td>0.86</td>
</tr>
<tr>
<td>Serum β₂-microglobulin &gt;3-0 mg/l</td>
<td>1.84 (1.18–2.88)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cold agglutinins</td>
<td>1.49 (0.58–3.81)</td>
<td>0.41</td>
</tr>
<tr>
<td>Cryoglobulins</td>
<td>1.05 (0.41–2.70)</td>
<td>0.92</td>
</tr>
<tr>
<td>Bone marrow involvement ≥50%</td>
<td>1.48 (0.94–2.34)</td>
<td>0.10</td>
</tr>
<tr>
<td>Symptomatic hyperviscosity</td>
<td>0.58 (0.29–1.17)</td>
<td>0.12</td>
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<tr>
<td>Serum IgM level 0–10 g/l</td>
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<td></td>
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<tr>
<td>Serum IgM level 10-01–20 g/l</td>
<td>0.51 (0.26–1.01)</td>
<td>0.05</td>
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<td>Serum IgM level 20-01–30 g/l</td>
<td>0.53 (0.26–1.08)</td>
<td>0.08</td>
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<tr>
<td>Serum IgM level 30-01–40 g/l</td>
<td>0.69 (0.35–1.39)</td>
<td>0.30</td>
</tr>
<tr>
<td>Serum IgM level 40-01–50 g/l</td>
<td>0.86 (0.36–1.39)</td>
<td>0.74</td>
</tr>
<tr>
<td>Serum IgM level 50-01–60 g/l</td>
<td>0.86 (0.32–2.30)</td>
<td>0.77</td>
</tr>
<tr>
<td>Serum IgM level &gt;60 g/l</td>
<td>0.80 (0.27–2.34)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
Age, sex, haemoglobin level, platelet count, serum β₂-microglobulin level, and serum IgM level are at the time of Waldenström macroglobulinaemia diagnosis.

Fig 3. Kaplan–Meier overall survival curves according to the development of symptomatic hyperviscosity. [Colour figure can be viewed at wileyonlinelibrary.com]
Dimopoulos et al, 2000). Of importance, patients without complaints of visual disturbances can have evidence of hyperviscosity identified (‘silent hyperviscosity’), particularly in the peripheral retina when a dilated fundoscopic examination is performed (Menke et al, 2009). Morphological changes in the retina attributable to hyperviscosity have been reported in WM patients with a serum IgM level as low as 29.5 g/l (Menke et al, 2006). Our data nonetheless support the recommendation of fundoscopic examination for WM patients with a serum IgM level >30 g/l to evaluate for signs of hyperviscosity and in all patients with suspected symptomatic hyperviscosity (Treon, 2015; Castillo et al, 2016).

To our knowledge, the risk of symptomatic hyperviscosity associated with a corresponding serum IgM level has not been previously evaluated. Our findings show the risk increases exponentially in response to increasing serum IgM level, consistent with the exponential increase in serum viscosity described when the serum IgM level rises above 30 g/l (Fahey et al, 1965). Modest increases in serum IgM level can therefore result in the rapid onset of symptomatic hyperviscosity. Importantly, patients with a serum IgM level >60 g/l are at high risk (370-fold) for symptomatic hyperviscosity. Two out of three patients with a serum IgM level >60 g/l developed symptomatic hyperviscosity in our cohort. Taken together, these findings support a serum IgM level >60 g/l as the serum IgM threshold for initiation of WM-directed therapy in otherwise asymptomatic patients.

The survival analysis demonstrates that the occurrence of symptomatic hyperviscosity does not affect the long-term prognosis of patients with WM. Two smaller retrospective studies have also reported similar results (Kyrtonis et al, 2001; Morel et al, 2009). A recent population-based study using the Surveillance, Epidemiology, and End Results (SEER) database reported the median survival of WM patients has increased over the last decade, despite an incurable disease course (Castillo et al, 2014, 2015). Some patients can have survival measured in decades, particularly those diagnosed at a younger age. In all, these data suggest patients with symptomatic hyperviscosity do not necessarily warrant more aggressive therapy, but rather appropriate and prompt control of serum IgM levels to prevent irreversible hyperviscosity-related injury.

Clinically, WM patients with symptomatic hyperviscosity or high serum IgM levels require careful management so as not to exacerbate serum viscosity. Plasmapheresis can rapidly reverse hyperviscosity-related symptoms and typically reduces the serum IgM level by 30–60% after 2–3 sessions (Menke et al, 2008; Stone & Bogen, 2012). Bortezomib-based regimens or ibrutinib (if available) may be appropriate therapeutic options in such a setting given the rapid reductions in serum IgM levels achieved with these agents (Treon et al, 2009, 2015). Rituximab should not be administered to patients with a serum IgM level >40 g/l due to the ‘IgM flare’ phenomenon (Ghobrial et al, 2004; Treon et al, 2004). Likewise, a similar effect can be seen with intravenous immunoglobulin (IVIG) replacement, which may be indicated for WM patients with recurrent infections on the basis of IgG and IgA hypogammaglobulinaemia (Yang et al, 2009; Hunter et al, 2010). Furthermore, cryoglobulins can cause marked temperature-dependent elevation of serum viscosity (Stone, 2009), and may precipitate the occurrence of symptomatic hyperviscosity at lower serum IgM levels. Caution should also be exercised when transfusing red cells in patients with high serum IgM levels (Treon, 2009; Castillo et al, 2016).

MYD88 and CXCR4 somatic mutations are present in 90–95% and 30–40% of WM patients, respectively, and have been shown to be determinants of disease presentation (Treon et al, 2012, 2014; Hunter et al, 2014; Schmidt et al, 2015). Our results demonstrate that the odds of symptomatic hyperviscosity are significantly higher for WM patients carrying a CXCR4 nonsense mutation, whereas the MYD88 mutation showed no association. These findings expand upon previous results, wherein higher serum IgM levels and rates of symptomatic disease requiring therapy, including symptomatic hyperviscosity, at the time of initial presentation were observed among WM patients carrying a CXCR4 nonsense mutation (Treon et al, 2014). The CXCR4 nonsense mutation that results from the introduction of a stop codon in the C-terminal domain showed more robust and prolonged AKT and ERK 1/2 signalling versus cells carrying CXCR4 frameshift mutations in preclinical modelling (Cao et al, 2015a,b), and potentially could contribute to altered serum IgM production, thereby increasing the propensity for symptomatic hyperviscosity.

The present study, however, is not without limitations. Despite the large number of patients with WM included, our cohort may not be representative of the general population due to the inherent selection bias associated with patients seen at a tertiary referral centre. In addition, serum viscosity levels were not available for most patients, though serum viscosity levels are often not reproducible and may lack correlation to serum IgM levels (Castillo et al, 2016). Finally, tumour genotyping for MYD88 and CXCR4 somatic mutations was only available for approximately one-quarter of the cohort, probably reflecting the recent discovery of these genetic aberrations.

In summary, the findings of our study show that patients with a serum IgM level >60 g/l are at high risk for symptomatic hyperviscosity. Appropriate therapeutic intervention could be reasonable in this patient population regardless of symptomatic status to prevent hyperviscosity-related injury.

Acknowledgements

Portions of this research were presented at the 9th International Workshop for Waldenström Macroglobulinaemia in Amsterdam, the Netherlands, on 7 October, 2016, and at the 58th American Society of Hematology Annual Meeting in San Diego, CA, on 4 December 2016.
Authors’ contributions

JNG, SPT and JJC designed the study. JNG and KM performed the data gathering. TD, IMG, SPT and JJC took care of the patients. ZRH, LX and GY performed the tumour genotyping of patients. JNG and JJC performed the statistical analysis. JNG, SPT and JJC prepared the initial draft. The final manuscript was read and approved by all the authors.

Disclosures

IMG received research funding and/or honoraria from Bristol-Myers Squibb, Celgene, Novartis and Takeda. SPT received research funding and/or honoraria from Janssen and Pharmacyciles. JJC has received honoraria and/or research funding from Abbvie, Biogen, Celgene, Gilead, Janssen, Millennium and Pharmacyciles. JNG, KM, TD, ZRH, LX and GY have no conflict of interest to disclose.

References


