The high risk of symptomatic hyperviscosity in patients with high serum IgM levels can be used to support initiation of treatment in Waldenström macroglobulinemia

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**Background**

Hyperviscosity syndrome (HVS) is a clinical feature that can be associated with Waldenström macroglobulinemia. Current consensus panel guidelines recommend initiating WM-directed therapy only for patients experiencing symptomatic HVS rather than when a specified serum IgM level is reached (Kyle et al. 2003). However, many clinicians initiate treatment for an elevated serum IgM in the absence of hyperviscosity-related symptoms to preempt the development of HVS. Empiric treatment for WM patients with high serum IgM levels has been proposed as a reasonable criterion for treatment initiation regardless of symptomatic status given the risk for hyperviscosity-related injury (Treon, 2015). We therefore sought to determine the serum IgM threshold for which the risk of HVS would be supportive of treatment initiation, as well as describe the risk factors and prognosis associated with developing HVS.

**Patients and Methods**

We identified 825 untreated patients who met the consensus diagnosis for WM (Owen et al. 2003), and who received care at our Institution between January 1999 and June 2016. Medical files were manually reviewed to identify cases of symptomatic HVS between the time of WM diagnosis and initiation of frontline therapy. Pertinent clinical data were gathered. The Cox proportional-hazard regression method was used to fit univariate and multivariate models for symptomatic HVS and overall survival. The time from WM diagnosis to development of symptomatic HVS, defined as the time in months between WM diagnosis and diagnosis of HVS, and the survival from WM diagnosis, defined as the time in months between WM diagnosis to last follow-up or death, were estimated using the Kaplan-Meier survival method; comparisons were made using the log-rank test. P-values $<0.05$ were considered statistically significant.

**Results**

**Figure 1.** Cumulative incidence of HVS from WM diagnosis.

**Figure 2.** Serum IgM levels at the time of symptomatic hyperviscosity.

**Table 2.** Predictive analysis for developing symptomatic HVS.

**Figure 4.** Kaplan-Meier survival curves according to hyperviscosity.

In the multivariate model, advanced age at WM diagnosis ($>65$ y.o.) was the only significant adverse prognostic factor for survival (Adjusted HR 3.98, 95\% CI 1.56-10.2; log-rank p=0.004).

All but one patient with symptomatic HVS received WM-directed therapy in response to developing symptomatic HVS; one patient refused treatment. HVS patients with a serum IgM $>6000$ mg/dL were more likely to receive emergent plasmapheresis versus those HVS patients with a serum IgM $\leq 6000$ mg/dL (77\% vs. 58\%; Fischer's exact p=0.04).

**Conclusion**

Patients with a serum IgM $>6000$ mg/dL are at a significantly increased risk for symptomatic HVS. However, development of symptomatic HVS does not adversely impact overall survival. Given the magnitude of the risk described herein for symptomatic HVS, a serum IgM $>6000$ mg/dL may reasonably be considered as a criterion for initiation of WM-directed therapy.