

**Clinical characteristics and treatment outcome of disease related peripheral neuropathy in Waldenstrom's Macroglobulinemia (WM).**

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**Background:** Peripheral neuropathy (PN) is a debilitating morbidity in WM, whose natural history and treatment outcome is largely unknown. **Methods:** We examined the incidence, characteristics, and treatment outcome of disease related PN in 900 WM patients. **Results:** 199 (22.1%) patients had disease related PN with a higher incidence in sporadic vs. familial WM (23.5% vs. 15.6%;  $p=0.02$ ). PN patients had lower serum IgM ( $p=0.02$ ), B<sub>2</sub>M ( $p=0.02$ ), and BM disease burden ( $p=0.001$ ). Among 122 PN patients evaluated for neuropathic antibodies, 24.5%, 1.64%, and 0.81% were positive for MAG, GM1, and sulfatide antibodies, respectively. Patients with neuropathic antibodies had lower serum IgM ( $p=0.0002$ ) and BM disease burden ( $p=0.001$ ) vs. non-PN patients. 13/61 (21.3%) patients examined for amyloid were positive, and only 1 had a neuropathic antibody. The median time to treatment for all PN patients was 9 months. Among non-amyloid related PN patients who received PP or IVIG as their first intervention, 29/42 (69%) and 1/8 (12.5%) reported symptomatic improvement, respectively. 151 PN patients received frontline CTX which consisted of an oral alkylator, nucleoside analogue or rituximab; or rituximab combination with a nucleoside analogue, cyclophosphamide, thalidomide or bortezomib. Of these, 71 (47%) and 8 (5.3%) had improvement or complete resolution of PN following CTX, respectively. Symptomatic improvements were more likely with non-amyloid related PN (48.5% vs. 15.4%;  $p=0.045$ ); in patients who achieved a major response, i.e.  $\geq 50\%$  reduction in serum IgM (79% vs. 35.5%;  $p<0.0001$ ); those who received earlier therapy, i.e.  $\leq 24$  months (57.3% vs. 42.5%;  $p=0.06$ ); and those who received rituximab combination vs. any monotherapy (59.3% vs. 37.0%;  $p=0.007$ ;  $p=0.06$  vs. rituximab alone). **Conclusions:** PN is a common morbidity, particularly among sporadic WM patients. PP for non-amyloid related PN is an effective interim intervention. Improvements in symptomatic neuropathy occur in half of PN patients following CTX, and are more likely to occur in WM patients with non-amyloid related PN, those who receive earlier therapy, combination therapy with rituximab, and who achieve a major response.