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**The role of proteasome inhibitors in the treatment of WM**

Proteasome inhibitors (PI) are active drugs in Waldenstrom's Macroglobulinemia (WM). Both as monotherapy and in combination with steroids and rituximab, high overall response rates (ORR) and long duration of responses can be seen. An important advantage of treatment with PIs is that onset of response is often rapid, which makes it an attractive agent if rapid response, e.g. in patients with hyperviscosity syndrome, is needed. Other than reversible thrombocytopenia, the risk of hematotoxicity is low and therefore PIs can be safely combined with cytotoxic chemotherapy or other targeted agents.

An important disadvantage of PIs is the incidence of treatment-induced peripheral neuropathy, which can lead to treatment discontinuation rates of up to 30% with the first in class PI bortezomib. Strategies to reduce the risk of PN are to use bortezomib subcutaneously and once instead of twice weekly, or to use less neurotoxic 2$^{nd}$ generation PIs such as carfilzomib and the oral agent ixazomib. The oral PI ixazomib combined with dexamethasone and rituximab has shown an ORR of 96% in treatment naïve (TN) patients and 71% in R/R WM patients with good tolerability. PIs can also be combined with btk-inhibitors (btk-I). The CZAR-1 study randomized patients between ibrutinib and ibrutinib in combination with carfilzomib and recently also an RCT of DRC +/- bortezomib was successfully completed.

In conclusion, PIs are active agents in TN and R/R WM. Second generation PIs have shown good tolerability with reduced neurotoxicity. Their exact role in the treatment algorithm of WM is however not clearly defined.