## Efficacy of carfilzomib/oprozomib in relapsed/refractory Waldenström's Macroglobulinemia.

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Proteasome inhibition has proven efficacy in the treatment of Waldenström's Macroglobulinemia. Bortezomib was first reported by Dimopoulos et al in 2005 as having significant activity (Haematologica 2005;**90**:1655-1658). However, Bortezomib frequently produces severe treatment-related peripheral neuropathy (PN; Ghobrial et al J Clin Oncol2010;**28**(8):1422-1428). Carfilzomib and oprozomib or epoxyketones-based proteasome inhibitors which do not demonstrate significant treatment-related PN. Treon et al reported in 2014 on 31 patients treated with the combination of carfilzomib/rituximab/dexamethasone demonstrating an overall and CR/VGPR responses in 87% and 36% of frontline WM patients, respectively (Treon et al J Clin Oncol2010;**28**(8):1422-1428). This activity appears to be independent of $MYD88^{L265P}$ or $CXCR4^{WHIM}$ mutation status. The incidence of PN was 3.2% (grade 2). In the relapse setting, there is a paucity of data. We reported a case series of seven patients with relapsed or relapsed/refractory: four patients treated at 20 mg/m2 then escalated to 70 mg/m2 and the other 3 patients 20 mg/m2 dose escalated to 56 mg/m2: all patients responded including 1 sCR, 2 VGPR, 3 PR and 1 MR (Vesole et al Leuk Lymphoma 2018; 59: 259-261). The overall major response rate was 85.7%, median time to response 2.4 months, median duration of response 14.3 months and median time to progression 19.8 months. The regimen was tolerated well: 6 patients reported at least 1 grade $\geq$ 3 adverse event yet only one patient discontinued treatment due to grade 2 peripheral neuropathy on day 386. Finally, oprozomib has been studied in WM. Ghobrial et al (Blood 2016; 128:2110) reported on the efficacy of two different oprozomib schedules: 300 mg/days 1, 2, 8, and 9 of a 14-day cycle (2/7 schedule) or 240 mg/day when administered on days 1-5 of a 14-day cycle (5/14 schedule). For response-eligible patients with WM, ORRs were 71% and 47% on the 2/7 (n=14) and 5/14 (n=17) schedules. The median duration of response was 35 weeks and 8 weeks, respectively, for the two schedules. Discontinuations due to adverse events were substantially higher in the 5/14 schedule (47% versus 20%). Of note, our center continues to treat two patients on this phase ½ trial now at 70 months and 72 months, one in a PR and the other in a VGPR. Due to GI toxicities, oprozomib has not been studied further for this indication. In summary, the epoxyketones (carfilzomib/oprozomib) are highly effective in relapsed and relapsed/refractory WM with manageable toxicity profile. We recommend the use of carfilzomib, at least 56 mg/m2, be considered instead of bortezomib due to the substantially higher incidence of peripheral neuropathy with bortezomib.