Does Bortezomib-Dexamethasone-Rituximab-Cyclophosphamide Play a Role in the Treatment of Waldenström's Macroglobulinemia?

TO THE EDITOR:

In the recent publication "Bortezomib-Dexamethasone, Rituximab, and Cyclophosphamide as First-Line Treatment for Waldenström's Macroglobulinemia: A Prospectively Randomized Trial of the European Consortium for Waldenström's Macroglobulinemia" by Buske et al,[1] 202 patients with Waldenström's macroglobulinemia (WM) were randomly assigned to receive dexamethasone-rituximab-cyclophosphamide (DRC) versus bortezomib-DRC (B-DRC). Buske et al should be commended on successfully conducting this large, randomized trial in a rare disease. The effort to focus on the development of a finite, combination therapy with the goal of achieving a prolonged progression-free survival (PFS) is greatly appreciated.

The outcome of this trial showed a modest increase in major response rate with B-DRC compared with DRC (81% *v* 70%) although practitioners should be careful to weigh the potential increase in toxicity and also consider these data in more detail before applying this regimen more broadly as a standard first-line therapy for all patients with WM, particularly with other highly effective therapies available.

In the modern era of WM therapy, Bruton tyrosine kinase inhibitors play a role in the first-line and relapsed settings because of high overall response rates, prolonged PFS, and satisfactory treatment tolerance,[2,3] but the finite duration of chemoimmunotherapy with high efficacy and the possibility of deeper hematologic responses maintain chemoimmunotherapy as a standard first-line therapy for WM. For these reasons, many patients are treated with DRC or bendamustine-rituximab (BR) in the first-line or relapsed setting on the basis of previous retrospective and prospective data.[4-8] Which chemoimmunotherapy regimen is preferred in WM is not definitively known although an argument could be made that for future studies, a backbone of BR should be considered on the basis of data showing an improved overall response rate with BR versus DRC (98% *v* 78%), as well as an improved time to next treatment (TTNT) and a PFS of approximately 62-70 months with BR[8,9] compared with a reported PFS of 35-52 months with DRC.[6,9] Although there are no data demonstrating an improved overall survival with BR compared with DRC, the potentially superior overall response rate, improvement in TTNT, and prolonged PFS should make BR the more suitable backbone chemoimmunotherapy to use for future trials. The addition of bortezomib to DRC in the trial by Buske et al[1] improved upon the backbone of DRC but with some additional toxicity, and without a direct comparison it is not clear that this quadruplet therapy is superior to BR.

Importantly, we must also consider the adverse effect profile of bortezomib in patients with WM. Twenty percent of patients with WM present with peripheral neuropathy, and up to 50% are affected by neuropathy during their disease course.[10] In this trial, patients with symptomatic neuropathy (grade ≥ 2) were excluded on the basis of the eligibility criteria. Of the 99 patients with no symptoms of peripheral neuropathy at the onset of B-DRC treatment, 18 patients developed a peripheral neuropathy and 13 patients required a dose reduction in bortezomib because of neuropathy. This rate of neuropathy would likely have been even higher if an additional 23 patients had not had dose reductions in bortezomib for other reasons.

In addition to the limited ability to use B-DRC in >20% of patients with WM with neuropathy, we must also consider the suitability of this regimen for 30%-40% of patients with WM with CXCR4 mutations. In this trial, molecular testing was limited and therefore leaves little room to draw robust conclusions, but of the 19 patients with known CXCR4 mutational status, it was noted that although major responses appeared to be higher in B-DRC versus DRC in those with CXCR4 mutations (71% *v* 50%), the overall response rates were similar (86% *v* 83%), PFS was not improved, and 14% of those with CXCR4 mutations progressed during treatment with B-DRC. This raises concerns regarding the ability of the addition of bortezomib to overcome CXCR4 mutations, and therefore, B-DRC may not be the optimal therapy for these patients. Future trials in WM should be designed with requirements for standard methods of molecular testing for each patient, including at least MYD88, CXCR4, and TP53 evaluation, to allow for clear conclusions about treatment efficacy in each subgroup of patients and improved patient care in specific subgroups of WM.

Although the work portrayed in this study demonstrated the feasibility of using B-DRC in WM, we still do not know if B-DRC provides any benefit over BR and there is still considerable work required to identify a regimen that can be more broadly applied to the WM population, including patients with peripheral neuropathy and those with CXCR4 mutations, and result in improved hematologic responses, prolonged PFS, and ideally improved overall survival.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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