Peripheral neuropathy in multiple myeloma patients receiving lenalidomide, bortezomib, and dexamethasone (RVD) therapy

Jakubowiak et al recently published promising results from a phase 1/2 study evaluating the second-generation proteasome inhibitor carfilzomib in combination with lenalidomide and dexamethasone (CRd) for the treatment of newly diagnosed multiple myeloma. Encouragingly, only 23% of patients experienced peripheral neuropathy (PN), supporting the hypothesis that bortezomib-induced PN may be an off-target effect and that carfilzomib is less neurotoxic.

However, we would like to comment on the rate of PN quoted in the accompanying editorial associated with the use of lenalidomide, bortezomib, and dexamethasone (RVD), which also has very promising efficacy, with a ≥ partial response rate of 100% versus 94% for CRd. Specifically, it was stated that 80% of newly diagnosed patients in the phase 1/2 study of RVD developed sensory PN after 4 cycles of therapy. In fact, the PN rate of 80% was reflective of the entire duration of treatment, with PN rigorously assessed during an 8-cycle induction phase, followed by maintenance with all 3 drugs for up to 2 years or more. The median number of treatment cycles was 10 and 59% of patients received ≥ 8 cycles of RVD therapy; when analyzed after 4 cycles, the rate of PN was 67%, almost all of which was grade 1 or 2 in severity.

Moreover, a similar phase 2 study conducted by the Intergroupe Francophone du Myelome in newly diagnosed multiple myeloma patients using 3 cycles of RVD induction before and 2 cycles of RVD as consolidation therapy after transplantation demonstrated a 68% rate of PN overall, with 55% developing PN during induction. No cases of ≥ grade 3 sensory PN were observed. A recent randomized phase 3 study comparing subcutaneous versus IV bortezomib for relapsed multiple myeloma revealed that subcutaneous administration was associated with a significantly lower rate of PN of all grades (38% vs 53%), as well as lower rates of ≥ grade 3 PN (6% vs 16%). All measures of efficacy were identical between the 2 groups. Therefore, although the use of subcutaneous bortezomib has yet to be formally evaluated in the context of the RVD regimen, the data would suggest that this should be similarly effective and have a significantly lower rate of PN.

Last, the majority of patients who experience bortezomib-induced PN can expect improvement in their symptoms after dose modification or drug discontinuation, with many achieving complete resolution to baseline.

In conclusion, with careful attention to symptoms and appropriate dose modification, the RVD regimen is associated with a significant but manageable rate of PN. Forthcoming clinical trials will provide critical insights into the comparative efficacy and toxicity of bortezomib- and carfilzomib-based regimens. Specifically, a phase 3 study comparing bortezomib and dexamethasone with carfilzomib and dexamethasone in patients with relapsed multiple myeloma will provide a prospective comparison of rates of PN, recognizing that reporting bias may confound comparisons in the absence of blinding. In addition, a planned intergroup study comparing RVD with CRd in patients with newly diagnosed multiple myeloma will allow the determination of efficacy and toxicity profiles of the 2 induction strategies and better define their respective roles in frontline therapy.

Peter M. Voorhees
Division of Hematology-Oncology,
University of North Carolina Lineberger Comprehensive Cancer Center,
Chapel Hill, NC

Jacob Laubach
The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Myeloma Center, Department of Medical Oncology,
Dana-Farber Cancer Institute, Harvard Medical School,
Boston, MA

Kenneth C. Anderson
The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Myeloma Center, Department of Medical Oncology,
Dana-Farber Cancer Institute, Harvard Medical School,
Boston, MA

Paul G. Richardson
The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Myeloma Center, Department of Medical Oncology,
Dana-Farber Cancer Institute, Harvard Medical School,
Boston, MA

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Correspondence: Peter Voorhees, MD, The University of North Carolina Lineberger Comprehensive Cancer Center, Physicians Office Building, 170 Manning Dr, Chapel Hill, NC 27599-7305; e-mail: peter_voorhees@med.unc.edu.

References

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