

Updates in Proteasome Inhibitors for Managing Multiple Myeloma



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Because recent research into novel systemic therapies for multiple myeloma keeps yielding promising results, clinicians are equipped with a wide variety of options for managing multiple myeloma. However, treating patients with relapsed or refractory multiple myeloma remains a challenge, and relying on standard-of-care proteasome inhibitors (PIs) is still an important strategy to consider.

Placement of PIs in the multiple myeloma treatment paradigm was the subject of a recent *Between The Lines*, part of an ongoing series hosted by CancerNetwork® in which experts discuss updates in cancer care. **Paul G. Richardson, MD**, clinical program leader and director of clinical research at the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute and the RJ Corman Professor of Medicine at Harvard Medical School, both in Boston, Massachusetts, sat down for a virtual talk with **Cristina Gasparetto, MD**, professor of medicine at the Duke University School of Medicine and a member of the Duke Cancer Institute in Durham, North Carolina, to discuss recent updates related to PIs for relapsed/refractory multiple myeloma.

Roundup of Current PIs

“With all the excitement that there is in multiple myeloma—including monoclonal antibodies, immunomodulatory drugs, cellular therapies, and other more novel small molecules [inhibitors]—it’s

important to remember our backbone agents include proteasome inhibition. This has been a mainstay of therapeutics in myeloma for the last 20 years,” Richardson stated.

The discussion began with a review of the 3 FDA-approved PIs. Gasparetto spotlighted carfilzomib (Kyprolis), which first received FDA approval in 2012.¹ The drug has since been approved in combination with other therapies, namely lenalidomide (Revlimid) and dexamethasone (Rd) based on results of the ASPIRE trial (NCT01080391) in which the combination improved overall survival (OS) vs Rd alone in relapsed or refractory multiple myeloma.² At the time, investigators reported that the combination yielded a median OS of 48.3 months compared with 40.4 months among patients assigned to Rd without carfilzomib (HR, 0.79; 95% CI, 0.67-0.95; 1-sided $P = .0045$).

Richardson continued by looking to bortezomib (Velcade), another PI that has seen success in multiple myeloma and was approved in 2003.³ Next, they turned to the most recently approved agent in this class and the first oral PI, ixazomib (Ninlaro), which was made available in 2015.⁴

“[Ixazomib] is an intriguing drug, because it’s effective, but we have some concerns about the power of this drug in different combinations,” said Gasparetto. “But definitely a very interesting and important drug in the field [of] myeloma.”

When considering use of all 3 agents,

Richardson added that the advantages of each must be weighed and placed in context of the specific needs of the patient being treated. Additionally, repeated use of the agents in recent years has helped clinicians make major strides in the understanding of adverse events management. “We’ve gotten much better at knowing how to manage these effects, be it cardiovascular in the context of carfilzomib or neurotoxicologically in the setting of bortezomib,” Richardson said.

Gasparetto and Richardson agreed that ixazomib offered a special advantage as an oral drug. “What’s so exciting about ixazomib is that as an orally bioavailable boronate peptide, that rapid-on, rapid-off pharmacology has always made it very attractive, particularly for our frailer patients,” said Richardson. The oral option has also been particularly helpful during the COVID-19 pandemic, he noted.

Benefit Reproducibility and Durability

Richardson then pointed to a “high degree of reproducibility” between results derived from phase 3 trials and real-world clinical results, especially in the case of ixazomib. Gasparetto said this is important given that reproducibility may be elusive in some settings, in part because patients may receive treatment in a trial that is not reflective of the real world. “There is a dichotomy here with how we treat a patient in academia versus what’s going on in the real world,” she said.

Richardson pointed to disease management as a real-world accomplishment that stands in contrast to the typical standard of minimal residual disease negativity that is used in academia or clinical research. “In relapsed/refractory disease, a disease control that’s associated with a high quality of life and minimal toxicity by virtue of effective therapy is a win,” he said, adding that progression-free survival (PFS) was a “somewhat underappreciated” marker of clinical benefit.

Recent Clinical Findings

Richardson turned to recently reported

final OS results of the phase 3 TOURMALINE-MM1 trial (NCT01564537), which showed that ixazomib plus Rd did not result in any additional survival benefit compared with Rd and placebo in patients with relapsed or refractory multiple myeloma (HR, 0.939; 95% CI, 0.784-1.125; $P = .495$). These final survival results, however, coincided with the longest median OS in any study so far of Rd-based treatments.⁵

“This means those patients assigned to the control group obviously had excellent salvage therapies. There was, of course, a significant PFS advantage to the triplet over the doublet,” Richardson said. “But it also points to another fact, which is that interpreting [OS] in the relapsed/refractory space in myeloma is increasingly complicated because it depends on salvage therapies.”

“We were looking for a prolongation; a durability of response,” said Gasparetto. “And of course, the [OS] ultimately is the major end point. [These results can be seen as both] good and bad: bad because we didn’t show that we could impact the [OS] with this combination; but also very good, because we can rescue patients with additional therapies.” One major question, she added, was whether this drug combination could work in the newly diagnosed setting.

In the phase 3 BELLINI trial (NCT02755597) of venetoclax (Venclexta) or placebo added to bortezomib and dexamethasone, treatment in the active therapy arm lengthened PFS but was linked with greater mortality overall when compared with placebo.^{6,7}

“What we’re seeing here is that the triplet generates PFS advantage in early relapse. Unfortunately, with the numerous options that are available, it doesn’t [always] mean the [OS] difference in terms of longer-term follow-up. Critically, this also tells us that the ixazomib platform, by virtue of its excellent tolerability, does not do harm later,” said Richardson.

One study published in 2020 aimed to determine feasibility of long-term PI use by way of transitioning certain patients who were treated as part of the US

MM-6 (NCT03173092) real-world study (n = 84) from bortezomib-based therapy to ixazomib plus Rd. Investigators reported that this strategy may allow patients to continue PIs for an extended time, ultimately improving outcomes.⁸

“The overall response rate is very respectable,” said Richardson. “But the [very good partial response] rate or better is a solid 55% [in patients who were transitioned to the new combination], and 26%, achieve complete remission.”

Gasparetto said the study included an older, frailer population than would normally be enrolled in many phase 3 trials. “The depth of the response improved with time without affecting the quality of life; they were able to sustain therapy for a prolonged period of time,” she said. “At the first this was not my first choice, but this is a very good choice for a population of patients with myeloma with other issues. They will now be able to sustain a more aggressive therapy. I’m pleasantly surprised.”

The discussion concluded with a look at updated results from the MM-6 study that were presented during the 2021 American Society of Hematology Annual Meeting & Exposition and indicated that response rates and PFS were further improved among patients who just received a diagnosis and were treated with an in-class transition strategy from bortezomib to ixazomib (n = 101). The overall response rate at a median follow-up of 18.5 months was 78% with a complete response rate of 32%.⁹

“With a longer follow-up on this study, reaching a deeper response and the fact that patients were able to sustain the therapy was very important,” Gasparetto said. Richardson noted that the complete response rate after 3 cycles was just 9%, but this tripled by the 18.5-month benchmark. The sustainability of the response, both experts agreed, is a foremost consideration when tailoring treatment to each individual. ■

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