Treatment of Multiple Myeloma: Finding the Right Combination

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In the past, multiple myeloma was a disease with grim prospects for survival, and few therapeutic options. Today we have a multitude of options, and the armamentarium will continue to expand.

The treatment of multiple myeloma is evolving rapidly. The development of immunomodulatory drugs (IMiDs) in the late 1990s and proteasome inhibitors (PIs) in the first decade of this century has dramatically changed the outlook for patients, as we began seeing response rates never before imagined. Today the so-called novel agents are no longer novel but standard of care, and are being joined by a host of new therapeutics. The use of next-generation IMiDs and PIs is further complemented by histone deacetylase inhibitors (HDACIs), monoclonal antibodies, selective inhibitors of nuclear export, and other agents. Clearly, the number of available new drugs to treat multiple myeloma has outpaced our understanding of the best way to incorporate them into our treatment regimens.

In this issue of ONCOLOGY, Dr. Nooka and Dr. Lonial effectively review the broad range of studies in multiple myeloma that are using the newest combination treatments.[1] Although the concept of combination therapy in oncology has been pervasive for some time in the care of patients with solid tumors and other hematologic malignancies, physicians had been reluctant to use drug combinations in multiple myeloma, due to high toxicity and little evidence of superior response. However, this was before the influx of newer, well-tolerated agents, so the concept of adding agents associated with a minimal increase in toxicity has re-emerged.

Another emerging concept in the management of multiple myeloma is the aim of deeper response—to the point of a minimal residual disease (MRD)-negative state. Prior to the advent of novel agents, complete hematologic responses were rare and the need to detect submicroscopic residual tumor was not a priority. With modern treatments, a majority of patients can achieve a complete response (CR), with many achieving a stringent CR. It is in this era of deep responses that more sensitive testing, including multicolor flow cytometry, allele-specific oligonucleotide polymerase chain reaction, and next-generation sequencing, have been developed to determine the presence of MRD. Most importantly, we have learned that MRD negativity and very deep responses translate into improved progression-free survival.[2]

In light of the benefit seen from deep hematologic responses, as well as the availability of well-tolerated agents with non-overlapping toxicities, most myeloma physicians agree that combination therapy is a logical step towards improving progression-free and overall survival. Questions remain, however, with regard to how many agents to use and how to combine the multitude of agents available. Doublet, triplet, and even quadruplet combinations have been evaluated and continue to be investigated. Lastly, while not covered in the review article, another greatly debated topic is the cost of these growing combinations.

As Nooka and Lonial outline in their comprehensive review, doublet and triplet combinations with IMiDs, PIs, alkylators, and corticosteroids have been compared, and improved outcomes are seen when three therapies are used rather than two, with minimal increase in toxicity. In fact, Figure 2 in their article highlights this point by recommending doublet therapy upfront only in patients who are frail, without any high-risk features. Even in frail patients, a modified triplet regimen should be considered when high-risk features are present.[3] In the relapsed setting, doublet therapy is only advised for frail patients who remain asymptomatic with standard-risk disease. In all other patients, especially those who are fit, triplet therapy is preferred.

When choosing the optimal triplet combination in the upfront setting, new information is now available to facilitate decision making. A study by Moreau et al, comparing a triplet containing an IMiD, a PI, and a corticosteroid vs one substituting the IMiD for an alkylating agent (bortezomib, thalidomide, and dexamethasone [VTD] vs bortezomib, cyclophosphamide, and dexamethasone [VCD]) demonstrated improved responses with VTD, the IMiD (thalidomide) and PI (bortezomib)–based combination.[4] These data provide guidance for myeloma patients and physicians alike to opt for an IMiD and PI–based combination as initial treatment, except when

specific circumstances (severe neuropathy, frailty) are prohibitive. In fact, this study may herald the decline of the CyBorD regimen (cyclophosphamide, bortezomib, and dexamethasone), which had traditionally been regarded as equivalent to the IMiD-plus-PI combination.

Besides the monoclonal antibodies SAR650984, elotuzumab, and daratumumab described in the review article, additional classes of agents have shown efficacy either as single-agent therapy or, more often, in combination with other therapeutics. Antimyeloma activity has been shown with HDACIs,[5] yielding improvements in both response rates and progression-free survival when these agent are used in combination with a PI and steroids, compared with combined treatment of a PI plus a steroid.[6] Serious adverse events are a problem with HDACIs, so further study is needed to identify a well-tolerated dosing schedule. Progress is being made on this front, and an intermittent dosing strategy appears to mitigate side effects.[7] New selective HDACIs are now being tested and appear to be better tolerated, with encouraging antimyeloma effects. Other agents with novel mechanisms of action are actively being investigated for the treatment of multiple myeloma, and these, too, appear to work well when part of a combination therapy approach.

As more advances in myeloma research are made and additional agents are discovered, more questions arise with regard to how to use our newest therapies. First and foremost, if three agents are better than two upfront, should quadruplet therapies be introduced early? Indeed, while this question was not discussed in the article by Nooka and Lonial, we know that several ongoing phase III trials are evaluating the addition of an antibody to the traditional RVD (lenalidomide, bortezomib, and dexamethasone) or VTD backbone. We are fortunate today not only to have a variety of agents to test in this setting, but also an outcome measure, through MRD testing, that provides a surrogate marker of improved results. However, the quest for MRD negativity must be undertaken with caution and placed into the proper context. We are still learning how sustained the MRD state should be to correlate with improved outcome. It remains to be discovered at what point an MRD-negative state may allow us to stop therapy. We must also recognize that MRD is a marrow-based test and that ultimately we may need a combination of MRD and imaging results to help us determine whether a given patient can truly be considered “MRD-negative.” One can anticipate that as more trials include MRD as an endpoint, the answers to these questions will become apparent.

In the past, multiple myeloma was a disease with grim prospects for survival, and few therapeutic options. Today we have a multitude of options, and the armamentarium will continue to expand. The article by Nooka and Lonial impressively covers the broad current treatment landscape for our patients with multiple myeloma, and brings to mind the words of Albert Einstein: “Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning.”

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Oncology (Williston Park). 30(5):466–467.

References:

1. Nooka AK, Lonial S. Novel combination treatments in multiple myeloma. Oncology (Williston Park). 2016;30:451-8, 464-5.

2. Avet-Loiseau H, Corre J, Lauwers-Cances V, et al. Evaluation of minimal residual disease (MRD) by next generation sequencing (NGS) is highly predictive of progression free survival in the IFM/DFCI 2009 trial. Blood. 2015;126:abstr 191.

3. O’Donnell E, Laubach JP, Yee AJ, et al. A phase II study of modified lenalidomide, bortezomib, and dexamethasone (RVD lite) for transplant-ineligible patients with newly diagnosed multiple myeloma. Blood. 2014;124:abstr 3454.

4. Moreau P, Hulin C, Macro M, et al. Bortezomib, thalidomide and dexamethasone (VTD) is superior to bortezomib, cyclophosphamide and dexamethasone (VCD) prior to autologous stem cell transplantation for patients with de novo multiple myeloma. Results of the prospective IFM 2013-04 trial. Blood. 2015;126:abstr 393.

5. Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and

deacetylase inhibitors and the biological basis of synergy in multiple myeloma. Mol Cancer Ther. 2011;10:2034-42.

6. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15:1195-206.

7. Kaufman JL, Zimmerman T, Rosenbaum CA, et al. Phase I study of the combination of carfilzomib and panobinostat for patients with relapsed and refractory myeloma: a Multiple Myeloma Research Consortium (MMRC) clinical trial. Blood. 2014;124:abstr 32.

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