

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Monoclonal Antibodies in Multiple Myeloma: Data From the 2015 ASH Meeting



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H&O What are the most important principles in the management of multiple myeloma?

SL In the past few years, treatment options for myeloma have increased and become more effective. It is now important to develop a management plan. Most patients (excluding those who are frail) begin treatment with a 3-drug induction regimen initiated at the time of diagnosis. Among these regimens, one that combines a proteasome inhibitor and an immunomodulatory drug (IMiD) will likely be superior to one that combines a proteasome inhibitor with oral cyclophosphamide (eg, bortezomib [Velcade, Takeda/Millennium]/cyclophosphamide/dexamethasone). This approach is supported by studies presented at the 2015 American Society of Hematology (ASH) meeting by Philippe Moreau, MD, and Brian Durie, MD.

Another important principle is the use of high-dose therapy in suitable patients undergoing transplant. Data presented by Michel Attal, MD, at the 2015 ASH meeting showed that overall survival was far superior when patients treated with the best induction available—for example, lenalidomide (Revlimid, Celgene), bortezomib, and dexamethasone (RVD)—also underwent transplant. Multiple trials have continued to demonstrate an improvement in overall survival for patients who undergo transplant.

Maintenance therapy is another important issue. The case can be made that, in general, patients should receive some form of maintenance therapy. Maintenance therapy can be tailored to the patient's genetic risk at the time of

diagnosis. For patients at standard risk, lenalidomide alone is associated with a good outcome, whereas for high-risk patients, RVD maintenance improves progression-free survival and overall survival. If a patient does not tolerate maintenance therapy, it is reasonable to discontinue it to improve quality of life.

A goal in the management of myeloma is to prolong the first remission for as long as possible. Research into genetics, genomics, clones, and subclones has shown that myeloma is most sensitive to treatment at the time of the initial diagnosis. The best chance for long-term disease-free control, or even cure, arises early. The way to maximize long-term outcome is not by using 1 or 2 drugs indefinitely, but to develop a treatment plan consisting of multiple drugs in combination or sequence.

H&O What are the unmet needs in multiple myeloma?

SL There are several unmet needs in multiple myeloma. It would be helpful to distinguish patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering disease who are likely to develop myeloma from those who are not. MGUS is a precursor disorder in which patients have the abnormal monoclonal protein, but without any evidence of organ damage. Only 1% of all patients with MGUS will progress to myeloma each year, but all myeloma patients had MGUS before developing myeloma. This distinction could help identify patients likely to benefit from early intervention.

Another unmet need is how to best manage high-risk patients, particularly those at the very highest risk. High risk is defined by genetics. Fluorescence in situ hybridization and gene expression profiling are the best ways to identify the abnormalities that define high-risk disease. Diagnosis and management continues to be a challenge for these patients, even with all the new therapies.

It is also necessary to determine the optimal duration of therapy. In general, the current approach is to treat continually until progression. However, as the ability to assess low levels of minimal residual disease improves, a goal will be to identify patients who can potentially stop treatment.

H&O What are some current insights into the pathophysiology of multiple myeloma?

SL A key insight is that myeloma is not a single disease. It is many diseases, based on genetic and genomic aberrations. Another insight is that, unlike most other cancers, myeloma continues with its “day job” throughout treatment, meaning that the cells continue to produce antibodies. This process of high-protein production, high-protein turnover, and high-protein secretion provides an opportunity to kill the myeloma cells. Some of the most effective treatments, such as proteasome inhibitors, IMiDs, and monoclonal antibodies, function not by disrupting the cancer but by targeting the normal plasma cell biology. The best treatment path forward will be based on an understanding of how to take advantage of the basic plasma cell biology as well as the mutations that are now being identified.

H&O What types of monoclonal antibodies are being used in multiple myeloma?

SL The 2 antibodies that are the furthest along in development are very promising. The older agent is elotuzumab (Empliciti, Bristol-Myers Squibb), which targets SLAMF7. This protein is present on plasma cells and on natural killer (NK) cells. Elotuzumab tags the plasma cell for recognition by the immune system, and it also activates NK cells by binding to them. This dual mechanism allows the combination of elotuzumab with other therapies, such as lenalidomide or pomalidomide (Pomalyst, Celgene), to achieve even more immune activation. Elotuzumab targets the plasma and NK cells, but more importantly, it activates the immune system, allowing the effector cells to trigger apoptosis.

A second class of monoclonal antibodies consists of the CD38 molecules. The only approved agent, daratumumab (Darzalex, Janssen) is thought to work through several different mechanisms. Like elotuzumab, daratumumab exerts antibody-dependent cellular cytotoxicity.

It also has complement-directed cytotoxicity and causes antibody-dependent cellular phagocytosis, which leads macrophages to induce apoptosis. Other potential mechanisms include direct signaling via the CD38 itself and immune activation through the suppression of regulatory T cells and myeloid dendritic cells. CD38 molecules in development include isatuximab and a morphogenesis antibody known as MOR202.

H&O Why are monoclonal antibodies a promising therapy for multiple myeloma?

SL The most exciting aspect of monoclonal antibodies is that they surmount the intracellular resistance mechanisms that render therapies such as chemotherapy and proteasome inhibitors ultimately ineffective. It is hoped that an immune-based approach will be effective in both standard-risk and high-risk myeloma.

H&O What clinical trial data support the use of monoclonal antibodies in multiple myeloma?

SL In the ELOQUENT-2 (Phase III Study of Lenalidomide and Dexamethasone With or Without Elotuzumab to Treat Relapsed or Refractory Multiple Myeloma) trial, the addition of elotuzumab to the combination of lenalidomide and dexamethasone improved progression-free survival vs the combination alone (19.4 months vs 14.9 months; $P < .001$). This benefit was apparent for patients with high-risk myeloma as well as standard-risk myeloma. The addition of elotuzumab also appears to increase the durability of response vs lenalidomide and dexamethasone alone. At the 2015 ASH meeting, an update of the ELOQUENT-2 trial presented by Meletios Dimopoulos, MD, showed an improvement in overall survival for the patients randomized to receive elotuzumab with lenalidomide/dexamethasone compared with the patients receiving lenalidomide/dexamethasone alone. Although the difference did not reach the prespecified statistical endpoint, the curves did separate, and the difference is striking. Long-term follow-up analysis is still needed to confirm this benefit.

Previous studies have shown that single-agent daratumumab is associated with a response rate of approximately 30%. At the 2015 ASH meeting, a trial presented by Torben Plesner, MD, showed that daratumumab in combination with lenalidomide was associated with a response rate of more than 80%. In a study by Ajai Chari, MD, the response rate exceeded 70% when daratumumab was combined with pomalidomide. These response rates reflect the synergy between these types of therapies. The IMiD and the monoclonal antibody work well together to kill myeloma cells through immune-mediated

mechanisms, which is exciting and provides hope for the management of high-risk myeloma.

Data were also presented for the monoclonal programmed death-1 antibody pembrolizumab (Keytruda, Merck). As a single agent, pembrolizumab does not have any activity in myeloma. However, when combined with lenalidomide or pomalidomide, pembrolizumab exerts fairly significant activity, as shown in trials presented by Jesus San Miguel, MD, PhD, and Ashraf Badros, MD, respectively. In addition, in the trial of pembrolizumab and lenalidomide, many of the patients were resistant to lenalidomide at enrollment. It therefore appears that the addition of pembrolizumab can overcome drug resistance. Although the myeloma cells may be resistant to an IMiD, the immune cells may not be. This important finding should lead to further research into combining IMiDs with immune-based therapies.

H&O How will these studies impact management of multiple myeloma?

SL These studies establish elotuzumab and daratumumab as part of the treatment armamentarium for multiple myeloma. Daratumumab in particular is very promising for patients with limited options. As a single agent, daratumumab works in 1 of 3 patients. Daratumumab is even more effective in combination with an IMiD. Elotuzumab is an option for patients who are progressing on lenalidomide maintenance or who have not received lenalidomide after transplant. The combination of elotuzumab, lenalidomide, and dexamethasone offer benefit in this setting.

H&O What are some areas of future research?

SL It will be necessary to determine the best way of combining these agents to formulate a rational approach to treatment. When I see patients in my clinic, I discuss induction therapy, transplant, and posttransplant maintenance. I map out a treatment plan for the first 2 to 3 years. The introduction of monoclonal antibodies raises important questions about their best fit within the traditional treatment approach. Are there certain times in the course of care that monoclonal antibodies will be more effective or less effective? It will be necessary to incorporate monoclonal antibodies into a planned treatment approach to avoid giving too many therapies simultaneously while administering the right agent at the right time.

Disclosure

Dr Lonial is a consultant for Millennium, Novartis, Celgene, BMS, Janssen, and Onyx.

Suggested Readings

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