ADVANCES IN LLM

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

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Updates in the Treatment of Multiple Myeloma

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H&O How are the survival data evolving in multiple myeloma?

JB Current reports have demonstrated an extension in survival by 2–3 years, from an average of 3–5 years to at least 5–7 years. We recently published a retrospective review of 300 multiple myeloma patients treated with zoledronic acid who showed a 5-year survival of 69% and median overall survival (OS) of nearly 11 years (131 months). We are currently updating data from our own patients, and I anticipate even greater survival improvements once the final results are in.

Furthermore, a lot of the survival data are generated from tertiary centers where patients are not cared for directly. This can be quite misleading in terms of what the actual survival is in a real community-based practice. I do think it is different when you have a center where a patient comes in once a year. They have to be motivated and well enough to get there, and I do not think that is necessarily representative of patients in the general practice community.

H&O What are some promising new targets?

JB A lot of work is being done on lookalike drugs that cover the same targets, such as the recently approved carfilzomib (Kyprolis, Onyx Pharmaceuticals), which is similar to the proteasome inhibitor bortezomib (Velcade, Millennium Pharmaceuticals). Another promising example is pomalidomide, a chemical analogue of lenalidomide (Revlimid, Celgene) and thalidomide (Thalomid, Celgene), which appears to have a much greater potency in stimulating the proliferation of T cells as well as increasing natural killer cell activity. Pomalidomide seems to be able to overcome resistance to lenalidomide in early phase I and II trials and has also demonstrated notable activity when used in combination with a number of anti-myeloma agents.

There are also a variety of new classes of drugs, such as the histone deacetylase (HDAC) inhibitors. Romidepsin (Istodax, Celgene) and vorinostat (Zolinza, Merck) have received approval by the US Food and Drug Administration (FDA), while panobinostat is in clinical development. Although there may be some modest activity when combined with drugs like bortezomib and dexamethasone, HDAC inhibitors have shown limited results when used alone. The side effects are often high, and the therapeutic ratio does not appear to be as promising as previously anticipated. Nevertheless, this class of drugs is a work in progress, and I think further studies are warranted.

Elotuzumab is a humanized monoclonal antibody targeted against the cell surface glycoprotein CS1, which is highly expressed on multiple myeloma cell lines. Although it has not been shown to harbor activity as a single agent, it demonstrated notable response rates as combination therapy in a phase II study of patients with relapsed or refractory multiple myeloma. A phase III clinical trial (ELOQUENT-2 [Phase III Study of Lenalidomide and Dexamethasone With or Without Elotuzumab to Treat Relapsed or Refractory Multiple Myeloma]) is under way to assess the combination of elotuzumab with lenalidomide and dexamethasone compared to the latter 2 drugs for patients with relapsed multiple myeloma.

H&O Why is it important to continue developing treatment options for patients with relapsed disease?

JB Multiple myeloma remains an incurable disease, and in most cases, the duration of remission is limited. Therefore, it is imperative that we continue investigating novel drug combinations and develop more clinical studies for patients who relapse after treatment or become refractory to treatment. Continually providing patients with new options is crucial.

We will be presenting updates later this year at the 54th annual meeting of the American Society of Hematology, demonstrating that carfilzomib is a potentially safe and effective replacement for bortezomib for patients with multiple myeloma who progressed while on treatment with bortezomib-containing regimens. Responses to carfilzomib thus far have been robust, rapidly achieved, and durable in regimens combining carfilzomib with a wide range of drugs and drug classes, including alkylating agents, anthracyclines, immunomodulators, and glucocorticoids. The fact that carfilzomib has demonstrated significant activity for patients who have been failing bortezomib combination therapies and have been treated with many other options is very hopeful.

H&O How is maintenance therapy currently used?

JB Three recently published studies support the use of lenalidomide maintenance therapy in multiple myeloma. Attal and colleagues in the Intergroupe Francophone du Myelome (IFM) evaluated lenalidomide maintenance therapy post-transplant, and found that progression-free survival (PFS) was 41 months and 23 months with lenalidomide and placebo maintenance, respectively (P<.001). However, there was no significant difference in OS. Similarly, a study by Palumbo and colleagues compared melphalan-prednisone-lenalidomide induction followed by lenalidomide maintenance (MPR-R) with melphalan-prednisone-lenalidomide (MPR) or melphalan-prednisone (MP) followed by placebo in multiple myeloma patients aged 65 years or older. At a median follow-up of 30 months, PFS was significantly prolonged after MPR-R (31 months) versus MPR (14 months) or MP (13 months). Importantly, the PFS benefit occurred in patients aged 65–75 years, but not in older patients. To date, there is no difference in OS. In the third trial by McCarthy and coworkers, lenalidomide maintenance therapy, initiated 100 days after hematopoietic stem cell transplantation, was associated with more toxicity and second cancers but a significantly longer time to disease progression and markedly improved OS for patients with myeloma. Bortezomib-based maintenance regimens may also optimize myeloma treatment. Whether or not bortezomib maintenance therapy provides a survival advantage remains unclear, although I believe it has the potential to do so. We must await results of randomized trials to confirm its role in maintenance therapy.

H&O What are some recent discoveries?

JB We just uncovered a new marker for myeloma. B-cell maturation antigen (BCMA) levels in the blood are elevated in multiple myeloma patients and are associated with disease status and OS. This biomarker may also be applicable to treating patients with lymphoma and chronic lymphocytic leukemia, although that remains uncertain. The study was published in the September issue of the *British Journal of Haematology*.

H&O What work is being done to improve quality of life for myeloma patients?

JB Nearly 80–90% of multiple myeloma patients develop osteolytic bone lesions that can cause debilitating bone pain and fractures. Intravenous bisphosphonates, particularly zoledronic acid, continue to provide benefit as the preferred bone-targeting therapy in this disease. New techniques utilizing novel agents and plasmapheresis are being developed for overcoming kidney failure more quickly. There are also some drugs that may help with a major problem in myeloma, which is trouble with mental function and mental fatigue. I think that the ability to overcome mental fatigue will be a major breakthrough for improving quality of life in patients with multiple myeloma, and we are currently evaluating psychostimulants such as armodafinil in randomized trials.

H&O What are the biggest remaining challenges?

JB A big challenge is the balance between treating multiple myeloma aggressively enough to be effective while minimizing side effects and maximizing quality of life for patients. Achieving long-term survival should not be the only goal in myeloma treatment. We must also focus on relieving the symptom burden that is caused by both the disease itself as well as aggressive treatments.

H&O What do you think the future holds?

JB I think the future is very bright. Although multiple myeloma remains an incurable disease, new therapeutic agents have provided encouraging results as viable treatment options, despite the fact that all patients relapse at some point. The development of new myeloma targets is a very active area of research. Second-generation proteasome inhibitors and newer IMiDs are evolving clinically and have demonstrated the ability to overcome resistance to similar agents in these same drug classes. Overall, I think that patients with multiple myeloma will continue to live longer with much better quality.

Suggested Readings

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