

ADVANCES IN LLM

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

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Multiple Myeloma: Treatment Updates



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H&O What are the current survival rates in multiple myeloma? What factors may affect data?

JB The problem with reports of survival rates in multiple myeloma is that much of the data are generated by sites where the patients are not receiving primary therapy. It is a rather biased group, as patients have to be well enough and have the financial means to travel to the site. Thus, any reports on survival rates among these patients are not necessarily representative of the general multiple myeloma patient population.

We are updating our own survival data. The preliminary data show average survival to be well over 10 years among the myeloma patients we treat, which is astounding. We will have a more exact number within the next 1 to 2 months. The current average 5-year survival is approximately 80%, whereas 10 years ago, it was around 10% to 20%. It is clear that some amazing strides have been made.

H&O What are some new agents in development?

JB The most promising agents in development appear to be the antibody-based treatments and conjugates involving proteins on the outside of myeloma cells (CD38, CD138, and CS-1). Our group and others are working on those in the laboratory with great success, although they remain in early preclinical development. I think that future research is going to focus on more specific therapy that attacks only the myeloma. We often refer to the drugs we currently have as being targeted, but they are not targeting the cancer cells alone. Ultimately, we are trying to develop curative therapy; for now, we are dealing with myeloma mainly as a chronic

disease that can be controlled for many years. Greater molecular understanding of the disease is a key to further progress.

New proteasome inhibitors are being developed with the aim of improving activity, tolerability, and overall convenience. Ixazomib citrate (MLN9708) and oprozomib are investigational agents that have shown similar selectivity and potency compared with bortezomib (Velcade, Millennium) and carfilzomib (Kyprolis, Onyx) in preclinical studies. These are the first oral proteasome inhibitors to enter into clinical investigation in multiple myeloma.

Elotuzumab (Abbott/Bristol-Myers Squibb) is a humanized monoclonal antibody that targets the cell-surface protein CS-1, which is highly expressed on multiple myeloma cells. The drug is able to induce the breakdown and death of certain cancerous cells. The combination of elotuzumab with lenalidomide (Revlimid, Celgene) and low-dose dexamethasone is being further studied in 2 phase 3 trials. The first trial (ELOQUENT-2; NCT01239797) is being conducted in patients with relapsed or refractory myeloma and has completed enrollment. The second trial (ELOQUENT-1; NCT01335399) is being conducted in patients with newly diagnosed, previously untreated myeloma and will enroll up to 750 patients.

H&O How are newly-approved drugs evolving?

JB Two recently approved drugs, pomalidomide (Pomalyst, Celgene) and carfilzomib, are showing great promise as part of combination treatments. Both agents have already been tested in clinical trials with a wide variety of effective anti-myeloma drugs, including corticosteroids and chemotherapy.

Recent findings from our own group demonstrated 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. Carfilzomib has also been used in newly diagnosed myeloma patients in combination with lenalidomide and dexamethasone, as well as chemotherapeutic agents like cyclophosphamide and melphalan, with high response rates. These results provide the opportunity for multiple myeloma patients to receive additional effective and well-tolerated treatment regimens.

In early trials, pomalidomide seems to be able to overcome resistance to lenalidomide in multiple myeloma patients. The drug has also demonstrated notable activity when used in combination with a number of antimyeloma agents. At the 2013 American Society of Clinical Oncology annual meeting, we presented data that showed the high level of efficacy of pomalidomide when combined with pegylated liposomal doxorubicin (Doxil, Janssen Products, LP) and dexamethasone. Other groups are evaluating this agent in combination with different drugs, including bortezomib and carfilzomib.

H&O What is now known about drug resistance?

JB I think that if we understood this topic fully, we would be in a much better position to target pathways that lead to drug resistance, thereby preventing it from happening altogether. It is important for physicians to recognize that resistance to one drug does not imply that patients will necessarily be resistant to others within the same class. For example, patients who are refractory to bortezomib have responded to carfilzomib, and those whose disease has failed to respond to lenalidomide may respond to pomalidomide. This greatly increases opportunities for patients to live longer.

In addition, patients failing bortezomib or carfilzomib with one chemotherapeutic agent often respond to combinations using other agents. The same holds true for immunomodulatory combination failures.

H&O What are some newly identified markers?

JB We recently uncovered a new marker for myeloma, known as B-cell maturation antigen (BCMA). Myeloma patients have elevated BCMA levels in the blood, and elevated levels are associated with advanced disease status and reduced overall survival. This biomarker may be able to serve as another way in which we will be able to follow patients with a simple blood test.

Additional markers being utilized include the serum free light chain, as well as an assay in development involving measurement of the patient's serum heavy and light chains. This latter test will allow us to measure the specific heavy and light chain being produced by the malignant clone vs the normal, healthy ones.

H&O What are some ongoing efforts regarding the biology of myeloma and personalized therapy?

JB I think we are at a point where we can identify which patients are at a higher risk, but we cannot yet know what to treat them with in order to help them overcome that risk. There is a strong unmet need to develop personalized therapies for myeloma patients based on their specific genetic abnormalities.

Certain chromosomal abnormalities have been associated with poor prognosis among myeloma patients, such as t(4;14), t(14;16), t(14;20), and del(17p13). The next step is to develop treatments that target these abnormalities, as well as those that cause drug resistance, especially at earlier stages in the disease. Until we actually have targeted therapy that only impacts the malignant cells in multiple myeloma patients, combination therapies will be key in the longer-term in order to overcome drug resistance and improve responses among all patients.

H&O What are the biggest remaining obstacles?

JB The biggest obstacle is our failure to fully appreciate the side effects of these drugs and that changes in doses and schedules of these agents can greatly reduce these untoward effects. It is often unnecessary to use these agents at their full dose in order to achieve their full benefit for patients in the long term. In fact, these drugs should not always be administered at full dose; although such an approach may eradicate the myeloma, the patient's quality of life suffers greatly from these so-called "more aggressive" treatments. We must learn how to administer truly targeted therapy that will result in the least amount of toxicity possible so that patients can maintain optimal quality of life.

H&O What is your outlook for the future?

JB I think the future is very bright for our multiple myeloma patients with all of these new options. As long as patients do not become overtreated, they will have a variety of therapeutic options to work with in the long run. The opportunities are plentiful, thanks to the development of new regimens involving already approved drugs as well as agents that are in development but are not yet approved for clinical use.

Suggested Readings

Jakubowiak AJ, Benson DM, Bensinger W, et al. Phase I trial of anti-CS1 monoclonal antibody clotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma. *J Clin Oncol.* 2012;30(16):1960-1965.

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