

New Developments in Multiple Myeloma Management

by James R. Berenson, MD

The treatment of multiple myeloma (MM) has changed greatly in the past few years, thanks to the development of a variety of new treatment options. These include not only chemotherapy but now a variety of more targeted therapeutic options, including thalidomide (Thalomid®), bortezomib (Velcade®), arsenic trioxide (Trisenox®) and likely to be available soon, lenalidomide (Revlimid®). Notably, recent studies show that these agents are more active when combined with older standard treatments such as chemotherapeutic drugs or steroids. **Laboratory and clinical studies have demonstrated that smaller doses of the new and older agents administered together lead to enhanced anti-MM effects.** Since these newer agents are associated with different organ toxicities than the older agents, these combinations have shown excellent tolerability and safety.

Thalidomide was first evaluated in MM in the late 1990s because of its ability to prevent blood vessel development, its so-called “antiangiogenic” effects. However, its anti-MM effects are probably the result of a multitude of additional properties, such as how it directly affects tumor cells, the bone marrow microenvironment that the tumor grows in, and the person’s immune system.

Thalidomide alone produces approximately a 30 percent response rate with the average duration of response lasting one year. However, the addition of steroids to thalidomide leads to much higher response rates (approximating 65 percent).

A recently completed study comparing this combination to steroids

alone in previously untreated MM patients showed a higher response rate in the group receiving thalidomide with steroids, although survival was not followed as an endpoint. The effects of this drug on the central and peripheral nervous system are well-known.

Although the agent is active, one has to weigh the side effects in terms of when to use this agent, for how long, and what dose to maintain once the person achieves a response. Unfortunately, there is little data to evaluate the dosage and duration of treatment among responding patients. Most MM experts treat people until the maximum response is reached and then begin to reduce doses because of the likelihood of irreversible nerve-related problems that occur with its prolonged use at higher doses.

The other significant side effect is its association with blood clots, particularly in the legs and more seriously in the lungs. There have been attempts to reduce this risk with blood thinning agents such as Coumadin® and/or low molecular-weight heparin. Other researchers have tried low doses of oral aspirin with a reduction in risk as well.

Recently, a newer analog of thalidomide known as lenalidomide has shown similar response rates to thalidomide as a single agent and may reduce nervous system-related problems. There have been two large randomized studies comparing this newer agent with steroids compared to steroids alone, suggesting that this combination leads to higher response rates, with a longer time to progression than dexamethasone alone. However, overall survival data from these studies is not yet available. This drug is also being combined with a number of other anti-myeloma agents in clinical trials.

Bortezomib alone has been approved by the U.S. Food and Drug Administration based on a single arm study and shows a response rate as a single agent of approximately 30 percent in previously treated patients. It has also been approved as a second line therapy for myeloma based on a large randomized study comparing

this drug to standard dexamethasone. Unfortunately, this agent also may cause nerve-related problems, which actually may be painful in some people. However, this is largely reversible, although the time to reversibility may take months.

Importantly, bortezomib also improves responses to other drugs such as melphalan or liposomal formulations of doxorubicin. Recent studies show that small doses of bortezomib when combined with melphalan or liposomal doxorubicin (Doxil®) are associated with very high response rates with long duration and minimal toxicity. Bortezomib as a single agent in the first line setting has also shown a high response rate. A number of studies are evaluating this drug combined with other agents, including melphalan and Doxil in the front line setting.



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Arsenic trioxide has recently shown some modest activity as a single agent in MM. However, when combined with melphalan along with vitamin C, it has shown a high response rate in people with heavily pretreated MM. In addition, recent early studies suggest activity when this drug is also combined with bortezomib. The drug is also being evaluated with other drugs, such as thalidomide and Doxil.

Overall, there is certainly an increasing number of options for people with myeloma to choose from in their battle against this disease. These options are not only leading to longer lives for people with myeloma, but better quality of life as well. Stay tuned.

Editor's Note: James R. Berenson, MD, is the chief executive officer and president of the Institute for Myeloma & Bone Cancer Research (www.myelomasource.org). Dr. Berenson has authored and co-authored many books, articles and abstracts in medical journals and has served as a member, advisor or director of over 40 organizations. ■