The role of carfilzomib in myeloma

Myeloma Today in conversation with Dr. David S. Siegel

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You are working with carfilzomib, a secondgeneration proteasome inhibitor. How does this compound differ from bortezomib?

Proteasome inhibition affects expression of a number of proteins involved in the cell cycle, causing apoptosis in myeloma cells. The first proteasome inhibitor that became commercially available for use in myeloma is bortezomib (VELCADE®), which is a boron salt. Bortezomib is a "competitive" inhibitor of the proteasome. This means that while bortezomib is around, the proteasome is inhibited, but as soon as the levels of bortezomib are reduced, the proteasome resumes its activity.

In contrast to bortezomib, which has an effect on myeloma cells that is reversible, carfilzomib targets the same proteasomes irreversibly. We call carfilzomib a "noncompetitive" proteasome inhibitor. Carfilzomib, which is an epoxyketone, binds to and destroys the proteasome permanently. So while both bortezomib and carfilzomib hit the same target, they hit it in very different ways.

In the myeloma setting, how is the permanent impact of carfilzomib preferable to the temporary action of bortezomib?

Proteasomes are essential to cells, so inhibiting proteasomes is a potentially dangerous thing. While carfilzomib targets the proteasome selectively, we certainly did not know until it was tested that carfilzomib would turn out to be the more effective proteasome inhibitor. But the data gathered from numerous investigations of carfilzomib is showing that it is at least as effective against myeloma as bortezomib, if not more effective, and it has a better toxicity profile.

Part of the rationale for developing a new drug is to improve efficacy and/or tolerability, as well as to address potential drug-resistance to the firstgeneration drug. In other words, in patients who have become resistant to bortezomib, the use of a new proteasome inhibitor such as carfilzomib might overcome the resistance to bortezomib.

What have the studies shown about carfilzomib?

Carfilzomib has generated very positive data in several early-phase studies. The phase I clinical trials of carfilzomib showed that it was well-tolerated. In addition, the low rates of peripheral neuropathy (PN), a side effect of several myeloma therapies, make carfilzomib very much different from bortezomib and the other boronated proteasome inhibitors.

In a phase I study of 19 patients who had relapsed following or became refractory to previous therapies, treatment with

carfilzomib resulted in an overall response rate (ORR) of approximately 17%, indicating that singleagent carfilzomib is active in relapsed/refractory myeloma.

An ongoing phase Ib multicenter, open-label, single-arm, non-randomized dose escalation clinical trial of carfilzomib plus lenalidomide and low-dose dexamethasone in relapsed/refractory myeloma is studying four dose levels in order to evaluate safety and define the maximum tolerated dose (MTD) of this three-drug combination in patients who had failed 1-3 prior therapies, including prior treatment with lenalidomide or bortezomib.

What can you share with us about phase II and III clinical trials of carfilzomib?

The data from phase II trials of carfilzomib in myeloma have been presented at several major meetings, including the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the European Hematology Association (EHA). Carfilzomib has been shown to have excellent activity both in heavily pretreated patients and in those who were not. It is active in patients who have been previously treated with bortezomib and, more importantly, carfilzomib has been shown to be active in patients who are bortezomib-resistant.

There are now two ongoing phase II clinical trials investigating the efficacy, safety, and tolerability of carfilzomib as single-agent therapy in myeloma patients with relapsed/refractory disease. One ongoing phase II clinical trial is evaluating relapsed/refractory patients who have received prior treatment with bortezomib, and either thalidomide or lenalidomide, and are refractory to their last treatment. This study is open-label, single-arm, and non-randomized.

The second ongoing phase II clinical trial is an open-label, single-arm, non-randomized study testing the activity and safety of carfilzomib in relapsed/refractory patients who had 1-3 prior therapies and relapsed to the most recently-received therapy. There are two patient populations in this study: patients with relapsed and/or refractory myeloma who had not received prior bortezomib therapy and patients with relapsed and/or refractory disease following treatment with bortezomib.

Phase III clinical trials of carfilzomib will be opening at the end of 2010. One phase III international randomized clinical trial has been initiated to evaluate the safety and efficacy of carfilzomib in combination therapy with lenalidomide and low-dose dexamethasone compared to lenalidomide and low-dose dexamethasone alone in patients with relapsed myeloma.

I'd also like to mention that there are additional ongoing clinical trials with carfilzomib using a different route of administration. It seems that administering carfilzomib via infusion allows for higher doses of the compound to be used and we are hopeful that this will show even better responses in patients.

What are the prospects for this drug to become available to myeloma patients outside the clinical trial setting?

It is anticipated that the clinical trial data will support a new drug application (NDA) filing in the United Stated by the end of 2010, and we are certainly hoping for a fast-track approval by the Food and Drug Administration (FDA).

Is there anything you'd like to add in closing?

The carfilzomib clinical trials are continuing to mature and the data is continuing to be presented at the major hematology meetings. The data from all of the trials seem to confirm the initial presentation that carfilzomib is well-tolerated by patients and that it seems to have a high degree of activity against myeloma. It is also important to add that the patients who respond

to carfilzomib achieve responses that are quite durable. Carfilzomib is active in patients who are refractory to bortezomib and it seems to cause little to no PN, which is the main limiting factor in the administration of bortezomib. To be able to achieve a high degree of response that is durable without sacrificing quality of life is very exciting.

I have had wonderful experiences with patients on this drug, both in terms of toxicity and response. I had an experience with one patient, who was in hospice care at another major myeloma institution and came to us for the phase II trial of carfilzomib, who not only responded to treatment but started asking how soon he could return to work!

I have worked with carfilzomib in phase I trials, am now working with it in phase II trials, and will hopefully be involved with the phase III trials of carfilzomib in as well. We have had a tremendous amount of experience with carfilzomib in myeloma and I can tell you that it is a wonderful drug.