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Update on the Drug Development Pipeline for Myeloma

Convention Connection: American Society of Hematology Meeting
December 2011
Dr. James Berenson

Andrew Schorr:
Dr. Berenson, we're at the major meeting where so much in myeloma is discussed. What are you excited about?

Dr. Berenson:
In terms of what's happened during the past year, what's really exciting is now we're spreading even wider the new drugs available to myeloma patients. Not all of these are yet FDA approved, but they're into the docket at the FDA for review. So drugs such as pomalidomide, the newer version of lenalidomide, looks like another immunomodulatory agent. In the late 90s we had thalidomide. In the last five years we've had lenalidomide or Revlimid. Now it looks like we may have another option for patients who fail those two drugs.

Similarly, we've had Velcade for the last eight or nine years as the only proteasome inhibitor, only one in that class that we've been able to use effectively and FDA approved, but it's clear now that there are newer agents, a number of them in development. One in very late development, carfilzomib, is very active, especially being studied in the relapsed/refractory setting and even looks possibly more active than Velcade, although we don't know that for sure, but we are now seeing activity in patients that are very refractory to Velcade with a drug we thought was a twin. It turns out, no, it's not just like thalidomide and lenalidomide, failing thalidomide you get lenalidomide or failing lenalidomide you get thalidomide, we're now seeing Velcade failures who are dramatically responding to similar drug combinations with carfilzomib. We just opened up a whole opportunity for patients now to get a whole bunch of drugs. Because, remember, Velcade can be combined with a slew of different drugs. We're now seeing the same thing with carfilzomib. Even among failures again to Velcade combinations, this is a drug.

There are a lot of other drugs in early development in that same class, oral agents such as 9708 from millennium, the Nereus product, NPI-0052 and there also is a product from the group at Cephalon called CEP-18770. These are in early trials, some suggestions of activity in our laboratory and we published data and are publishing more. These are very exciting molecules. Some of them appear to overcome Velcade resistance, in the laboratory at least, like we've seen in carfilzomib and Velcade failures.

In terms of other types of drugs we have very good data only in the laboratory at this point, but which is a drug like DOXIL but in which you can give much more of this drug called INNO, or I-N-N-O, 206. It's a drug that is similar to doxorubicin but it's only released in the acid pH environment of tumors. So in your blood it's bound to albumin, it's inert, it doesn't work. But when it gets in the tumor, boom. So in our animal models

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you can give a lot more of this than conventional doxorubicin, and at least in the phase 1 trials you can give four and five times the amount of conventional doxorubicin or Adriamycin of this new agent. We hope to get into trials in myeloma combining it with either Velcade or carfilzomib in 2012.

There also are antibodies that are moving along, particularly the elotuzumab story. This is an antibody, the CS-1 or mucin which is expressed on myeloma cells and although as a single agent there's a very small activity, once you combine that, especially as presented here at the meeting, with lenalidomide or Revlimid and steroids, very high response rates. And whether that's adding to Revlimid and dexamethasone beyond what the activity of those two have alone we're going to see in large phase 3 trials. There's data with antibodies, the CD-138 that was just presented at the meeting, and there's also more data emerging with a number of other targets such as perifosine a PI3 kinase inhibitor, as well as a number of HDAC inhibitor studies, not alone but combined with either chemotherapy or Velcade. In the laboratory Velcade and these HDAC or histone deacetylase inhibitors are very active. Clinically there are now trials, phase 3s that are being done based on promising phase 2s that are being presented at this meeting as well.

There also is more data emerging that we and others have done with a drug called bendamustine, a drug very, very active in lymphoma and chronic lymphocytic leukemia. It's not been really well studied yet or until recently in myeloma, but we've done studies with Velcade that we're about to submit for publication presented at these meetings before and earlier this year at ASCO as well as with lenalidomide and steroids with bendamustine. It looks very promising.

And similar to what I said earlier with Thalomid to Revlimid to pomalidomide, we are seeing a similar story with alkylating agents, melphalan failures can respond to cyclophosphamide, and now we have another drug they can respond to, bendamustine in combination it looks like, with lenalidomide and steroids or in combination with Velcade.

So lots of new opportunities for patients now. We really have patients now in trials that have seen 15 and 20 prior regimens. We would have never dreamed about that even five years ago and patients with excellent quality of lives.

Andrew Schorr:
What about people living longer with myeloma? I know there's data presented here about that.

Dr. Berenson:
Yeah, I mean what's so exciting now is that 10 years ago the median survival was 30 months and we just published data--and remember that's data looking back the last decade--to add a one on the front end from a multicenter study. 130 months looking back. And I hope now over the next decade with all these new drugs we are seeing myeloma patients whose life span is really no different than their partners without myeloma. We're dealing with this as a chronic disease, ultimately of course hoping to cure it, but in the meantime the options keep growing for our patients.

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Andrew Schorr:
Sounds likes you have many tools now, more than ever before to treat myeloma, either approved drugs or ones that are coming.

Dr. Berenson:
Yeah. I think what's really important is there is no one way to take care of myeloma. They're all different. They all respond differently to different drugs, and we are trying to develop ways to identify who might be better treated with one regimen than another. Today we can kind of say who will probably not respond, but we can't say what you should get optimally based on genetics, chromosomes, gene array, proteomics. We're trying to get there. We are not there yet, but there are vast, different signaling pathways that can be attacked. That is, within the cell there are different ways that myeloma is stimulated to grow, stimulated to be resistant to different therapies, and we keep trying to tweak the cell to block those so the myeloma cell becomes more sensitive to our drugs we're using today.

Andrew Schorr:
Given that you have so many tools it would seem like it's important for a patient to have an active dialogue with their doctor, perhaps even a myeloma subspecialist.

Dr. Berenson:
Yeah, I think it's really important to recognize there is not one way to treat myeloma. There's not one algorithm. So if a doc is telling you that, you've got to be really careful. This is the only option. It is not. There are many ways to start and many directions to go if something should not work, even things as simple as increasing the dose. For example, we certainly see that with both thalidomide in our clinic and Revlimid. Patients get on a lower dose, they're doing fine, their disease begins to progress, you can simply increase the dose, and it will work. We would have never thought that true.

In a similar vein you would think that patients in the past who didn't respond to one drug in a class, say, melphalan, and then they get another drug in that class called an alkylating agent, cyclophosphamide or bendamustine, they respond. It's pretty amazing. And in a similar matter we thought that, oh, in five, seven years ago if you didn't respond to Velcade it's over, go to something else. You can combine Velcade with many different drugs safely and effectively, and it's really a matter of not giving up. There's more and more things to try in our patients today.

Andrew Schorr:
Sounds like you are optimistic.

Dr. Berenson:
Yeah. It's a really optimistic time for patients, and the beauty of it is my favorite photos of my patients are on the top of Kilimanjaro or over in China at the Great Wall or down at the Galapagos enjoying their lives, and that's really what it's about.

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