Highlights from the VIIIth International Myeloma Workshop

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Thalidomide: Mechanisms of Action and Clinical Outcomes

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DR. RICHARD LUTES: This is Dr. Richard Lutes, reporting from the Eighth International Myeloma Workshop in Banff, Alberta. We are discussing the final session, "Thalidomide, Mechanisms of Action and Clinical Outcomes," and we welcome Dr. Kenneth Anderson of the Dana-Farber Cancer Institute in Boston. Good morning Dr. Anderson. To start with can you just give us your overview of thalidomide please?

DR. KENNETH ANDERSON: Thalidomide is clearly a breakthrough in the therapy of multiple myeloma. Over two years ago it was used for the first time by doctors in Arkansas led by Dr. Bart Barlogie, and the observation in the clinic was that one-third of patients responded who literally responded to nothing else, in many cases having failed even two transplants. What's happened since is a flurry of activity to learn more about how to use thalidomide, to develop novel thalidomides that are even more potent that might have fewer side effects, and to rapidly move those new compounds from the bench or the laboratory to the clinic in trials with patients.

DR. RICHARD LUTES: Can you give us an overview of the role of thalidomide first in refractory patients, and second then as up-front therapy?

DR. KENNETH ANDERSON: Thalidomide in the initial study at the University of Arkansas achieved a response in approximately 30 percent of patients. As I mentioned earlier, many of these patients had failed high-dose therapy and were not treatable with any other conventional therapy. As is true of all the other agents we use to treat myeloma, when you use drugs earlier in the disease course, they work more effectively. Clearly tumor cells are sensitive to treatments early on after diagnosis, but they acquire drug resistance and have a more malignant phenotype with time. So thalidomide alone and together with other drugs, one of those being Decadron, has now been explored early in newly diagnosed multiple myeloma patients.

At this session, Dr. Donna Weber of M.D. Anderson in Houston and Dr. Vincent Rajkumar of the Mayo Clinic each reported on the combination of thalidomide and Decadron, both in refractory patients but more importantly in up-front or newly diagnosed patients with myeloma. In the refractory setting, 40 percent to as many as half of the patients responded to thalidomide and Decadron and surprisingly, some of these patients had failed either Decadron or thalidomide alone. But fully half of such patients will respond to the combination. Even more exciting, when you use thalidomide together with Decadron in the early part of the disease course shortly after diagnosis, the response rates are much higher in the range of 70 to as high as 80 percent rather than the third or 30 percent that we see in refractory disease.

DR. RICHARD LUTES: As almost any new drug becomes available, first it's used as a single and then in combination. And you mentioned the use of thalidomide with Decadron. What about other combinations?

DR. KENNETH ANDERSON: Well, Dr. Barlogie at this session has described his experience of utilizing thalidomide as part of a combination chemotherapy program which does include high-dose therapy and transplantation and I'll let him address the special issues in that context. However, also at this session both Dr. Mort Coleman from New York and also Brian Drurie from Los Angeles describe the use of a three-drug combination, Biaxin, an antibiotic, Decadron and thalidomide. And seemingly at both sites the response rates to Biaxin, Decadron and thalidomide appear to be higher than would have been expected with either thalidomide or thalidomide and Decadron alone. A note of caution however is to mention that there are not large numbers of patients treated and while there may be increased responses we need further studies to confirm that possibility. The other cautionary note I would add is that Biaxin does enhance the side effects that were noted related to thalidomide. The reasons this is occurring are unclear, but the observation suggests that Biaxin affects the way thalidomide is metabolized by patients. Still, we don't know yet, so a cautionary note is to wait for further clinical trials before we can firmly conclude that the combination is in fact better in a randomized way than either thalidomide alone or thalidomide and Decadron.

DR. RICHARD LUTES: Can you discuss your experience with the IMiDs please?

DR. KENNETH ANDERSON: We've had the privilege of working with the new more-potent thalidomide analogues. They are called immunomodulatory drugs or IMiDs. In the clinic these drugs are much more potent against myeloma cells than thalidomide is directly and also by inhibiting cytokines, altering interactions of the myeloma cell with the bone marrow microenvironment, inhibiting angiogenesis, and stimulating the patient's own immune response against myeloma. So given that exciting prospect we moved rapidly from the bench to the bedside in a clinical trial, a phase I clinical trial that began in our center last October. Dr. Barlogie also has a similar ongoing phase I clinical trial, both of us trying to determine the maximally tolerated dose of the new ImiD, the dose that would be defined as the one that is tolerated with an acceptable side-effect profile. And then we will rapidly move on to a larger study in which we having known the correct dose will be able to test in a large number of patients its actual efficacy. The excitement so far reported both by Dr. Barlogie and myself in this session is that even in a phase I setting where we're simply trying to determine the right dose, both of us have noted marked anti-myeloma activity. Seeing activity in a phase I trial of a new drug is extremely unusual, so for both of us and for all doctors and patients it's a source of great hope and optimism.

DR. RICHARD LUTES: Dr. Anderson, as the last speaker at this meeting, is there a take-home message that you'd like to leave for our audience?

DR. KENNETH ANDERSON: Yes, I think there is. This meeting was really a landmark meeting in multiple myeloma. These sessions here presented cutting-edge and novel information about the cell of origin of myeloma, events that are important in the progression of disease in terms of the disease biology. It explored for the first time in depth the role of the marrow microenvironment in the development and progression of myeloma and so dealt with factors such as angiogenesis and others. It updated high-dose therapy and conventional-therapy strategies, and it integrated some of the new technologies that are now

available such as gene array and proteonomics. I think one of the major take-home messages from this meeting is for the first time in perhaps 30 or more years we have novel treatments now that are designed not only to target the tumor cell but to target the microenvironment as well. And excitingly these agents work when high-dose therapy has failed, so they clearly are providing for us an opportunity to treat patients and offer hope where previously we have been unable to do so.

Also presented at this meeting were cutting-edge studies about immune treatments in myeloma, including vaccines and others that are finally progressing along quite well into the clinical trial setting. So I think the main take home message, and it would be for both patients, researchers, and caregivers alike is that the the spectrum of treatments that we are going to be having available for patients will vastly expand within the next year or two, and we can all expect a much better outcome for patients as a result.

DR. RICHARD LUTES: Thank you Dr. Anderson for your comments.

DR. KENNETH ANDERSON: Thank you.