

Highlights from the VIIIth International Myeloma Workshop

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Clinical Implications

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This is Dr. Richard Lutes, reporting at the Eighth International Myeloma Workshop in Banff, Alberta. We have the pleasure of speaking with Dr. Bart Barlogie of the Arkansas Cancer Research Center. Welcome Dr. Barlogie.

DR. BART BARLOGIE: Good morning.

DR. RICHARD LUTES: We'd like to discuss thalidomide, but first can you give us a short refresher course on the role of angiogenesis in myeloma?

DR. BART BARLOGIE: We really didn't know much about angiogenesis until thalidomide entered clinical investigation. Angiogenesis, of course, was stimulated through the exciting work of Judah Folkman's on endostatin and angiostatin, the two agents he evaluated in solid-tumor models. And then attention was also paid to some of the liquid tumors, the leukemias, and multiple myeloma. It became apparent to everybody's surprise that in the setting of extensive marrow involvement there was quite a bit of vascularity in patients with multiple myeloma. But the focus was then really intensified and research was intensified once thalidomide as an anti-angiogenesis drug entered the clinic, and it is now well established in multiple myeloma that the bone marrow microenvironment plays a very important role in the expansion and survival of myeloma cells.

Strictly antiangiogenic approaches have not been tested because whether it's thalidomide or some of the other putatively antiangiogenic drugs, they all seem to have other mechanisms of action as well. And until the time that strictly antiangiogenic molecules are entering the clinic such as endostatin, we will not really know whether this mechanism by itself will produce substantial antitumor activity.

DR. RICHARD LUTES: Can you summarize what we know currently about the mechanism of action of thalidomide?

DR. BART BARLOGIE: When we performed the early trial we were keen on demonstrating that patients who were responding to therapy had a reduction in the so-called microvessel density in the marrow. And we wanted to know what would happen in other patients who actually had a persistence of their increased microvessel density. More mechanistic investigations in various laboratories have shown that thalidomide exerts a number of other properties among which foremost are immunomodulatory properties. There are interactions that tumor cells have with the bone-marrow microenvironment, that is adhesion of myeloma cells to stromal cells as they are being disrupted by thalidomide. Thalidomide also has ways of making the

myeloma cells more susceptible to other agents including dexamethasone. So there's a whole plethora of effects that may all be operating in a given patient and may be different from one patient to another. And we now have model systems such as the SCID-Hu mouse into which one can implant primary human myeloma cells. One can begin to investigate how thalidomide and other agents actually work.

DR. RICHARD LUTES: I'd like to review the experience of yourself and others in the patients. First, let's talk about the role of thalidomide in refractory patients.

DR. BART BARLOGIE: After we reported in the *New England Journal* several years ago an activity of about 30 percent or 35 percent mainly in patients who had relapsed following one or two transplants, this experience has been confirmed worldwide. When we had a meeting about thalidomide that included Dr. Folkman, he said this was probably the fastest evaluation of a new drug in a systemic malignancy setting. He was very surprised how rapidly this caught on, and this is a testimony obviously to the dearth of new agents that we had in myeloma and to the activity of this compound in this disease.

We have since evaluated another hundred patients with multiple myeloma in the refractory disease state, and this is to be published shortly in *Blood* and confirming our earlier observations that about a third of patients respond, about 10 percent to 15 percent achieve complete remission, and some of these complete remissions are so durable that there are patients who relapsed from a transplant two or three years ago who are in a sustained state of disease control. We have recognized in those refractory disease trials that the dose actually does play a role. So in contrast to some of the studies currently ongoing in less heavily pre-treated patients, we have found that the dose of thalidomide does impact the response rate and response duration. Patients in our trial who received more than 400 milligrams had a higher response rate and longer duration of disease control.

There are several studies ongoing in various institutions evaluating thalidomide in conjunction with glucocorticoids in the refractory disease setting but also up front. We will be reporting at this meeting on thalidomide being combined with a combination of cytotoxic agents such as DT-PACE, an acronym that stands for dexamethasone, thalidomide, cisplatin, Adriamycin, cyclophosphamide and etoposide, and that combination is highly effective in the aggressive fulminant disease and brings about complete responses in about 20 percent of patients. We have gone on to evaluate the role of thalidomide for the up-front management of patients with myeloma in the randomized trial, total therapy to where we have an intensive remission induction followed by two cycles of high-dose therapy and followed by consolidation chemotherapy and then maintenance interferon. In up-front, all patients are randomized to receive 400 milligrams of thalidomide or not. The data are still blinded, we have treated over 300 patients and collectively for both arms combined the induction response is about 40 percent and after two cycles of high-dose therapy we are looking at a complete remission rate on the order of 70 percent. So these are very good numbers, and we should know probably in a year about the role or the contribution to the success that thalidomide makes.

DR. RICHARD LUTES: Dr. Barlogie, can you discuss IMiDs and how they differ from thalidomide and what the clinical trial status is currently?

DR. BART BARLOGIE: There are several congeners that have been designed to reduce the toxicity of thalidomide, which is dose dependent and comprises mainly sedative effects, polyneuropathy, constipation, tremors and the like. And they are acute-dose and cumulative-dose related. Celgene Corporation has designed a number of newer compounds. The the one currently in clinical trials is ImiD, and this has gone through a phase I/II evaluation at Dana- Farber Cancer Center and at our institution. At the Farber it is in the setting of refractory myeloma but without prior transplant, and at our institution in patients who have had previous thalidomide who have had a relapse following high-dose therapy.

We have now treated 12 patients on a dose-escalation schedule beginning at 5 milligrams daily to 10 milligrams, 25 and 50 milligrams. We have seen now at the 25- and 50-milligram dose, especially at the 50-milligram dose, three out of three responses, and overall we have seen six out of 12 patients who had more than 25-percent tumor-mass reduction. And we have seen three who had more than a 50-percent reduction. The sedative effects were nonexistent. Seven patients who had previously been treated with thalidomide were included in the trial. Some of them did have thalidomide-related neuropathy which did not worsen, which actually did improve on the IMiD investigation. So our current impression with relatively short follow-up of several months, two or three months, we see that the tolerance of the IMiD is much improved, and I think this drug holds great promise for eventual up- front management of myeloma patients as well.

DR. RICHARD LUTES: Excellent. Dr. Barlogie, given your extensive experience with thalidomide, are there specific patient-management issues that we should be aware of?

DR. BART BARLOGIE: Well, I think the most important issue is that thalidomide and other new agents be evaluated as part of the well- designed clinical trials. We and my colleagues working in the field of myeloma basic and clinical research see more and more patients who have been given thalidomide as up-front treatment by their primary physicians. And that is a practice I would not condone. I think we need to evaluate very carefully what thalidomide's role is. We don't really know the exact dosing, we know that lower doses, as low as 50 milligrams in newly diagnosed patients, in those with smoldering disease, do have an antitumor effect. We don't know whether it's important to keep a patient chronically on thalidomide or whether it is appropriate to have dose disruption for several months to allow for recovery from toxicities, and so on. The trials in Europe are under way to evaluate melphalan, prednisone vis a vis melphalan and thalidomide. The French myeloma investigators are looking at thalidomide as a maintenance strategy after transplant, and so on. I think there is clearly toxicity from thalidomide, and as the IMiD and other related compounds are being evaluated and show comparable or even greater antitumor activity, then they have a great potential to replace thalidomide. Whether these newer compounds work through similar mechanisms is currently being investigated.

DR. RICHARD LUTES: And can you tell us a little bit about Dr. Weber's presentation on thalidomide in untreated patients?

DR. BART BARLOGIE: Dr. Weber from the M.D. Anderson Hospital has together with Dr. Alexanian and her other colleagues used thalidomide in conjunction with dexamethasone based on trials initially in

refractory disease. And in a refractory disease setting thalidomide itself was no longer active, dexamethasone was no longer active, and the combination then was applied and brought about responses in about 20 percent or so of patients. When used up front Dr. Weber as well as Dr. Rajkumar of the Mayo Clinic have seen responses using 50-percent-reduction criteria in about 70 percent of patients. Complete remissions however have been rare, and so while the overall response rate using this 50-percent-reduction criteria is encouraging, the absence of complete remission is bothersome, and it would indicate that as with dexamethasone there is also in the case of thalidomide a tumor-resistant subpopulation that seems to escape the antitumor effects of thalidomide.

We have recognized in our program that chromosome 13 deletion is an adverse feature for benefit from thalidomide in both response and duration of response. And these kinds of qualitative studies have to be performed in order to determine at the genetic level which types of myeloma respond well to thalidomide and combinations of thalidomide, vis a vis those that need more intensive approaches. In our DT-PACE combination therapy program, the chromosome 13 deletion, present in about 20 percent of newly diagnosed patients, was not an adverse feature. So maybe there are means to overcome this very grave prognostic subgroup, which has a survival of a year to a year and a half. It is this group of patients that I think that would benefit when recognized up-front for new treatment approaches, where it would be appropriate to apply fundamentally new agents with even unknown mechanisms of action. These patients represent a well-defined subgroup so that it should be possible in short order to discover whether new agents have activity or not. And if they do have activity in such a high-risk setting then it can be hoped that they would be even much more effective in the more benign non-chromosome 13 deletion group.

DR. RICHARD LUTES: We want to thank you Dr. Bart Barlogie, Arkansas Cancer Center, for your comments.

DR. BART BARLOGIE: My pleasure, thank you.