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Panel Discussion

Dr. Joshua, *Symposium Chair:* Patients commonly ask about the risks associated with thalidomide and whether they should take the drug early or wait until relapse occurs. Will early or late therapy make a difference for patients?

Dr. San Miguel: It is probably better to start thalidomide treatment early, but we have no data to support that recommendation. Several studies are under way to address this question.

Dr. Harousseau: For patients who are not fit enough to undergo autologous transplantation, ongoing studies are evaluating the impact of thalidomide upfront in combination with melphalan/prednisone. We don't yet have the answer. Although there are differences in the response rates, and there will probably be differences in event-free survival, until now there have been no differences in survival, possibly because patients who do not receive early thalidomide can be salvaged by thalidomide at progression. It is also interesting to evaluate other new drugs such as bortezomib or lenalidomide as part of front-line therapy. One question is whether we should compare the combination of melphalan, prednisone, and bortezomib or lenalidomide with melphalan plus prednisone or lenalidomide with melphalan plus prednisone plus thalidomide. Another question to consider is the type of care that should be provided for elderly patients. Should they receive a combination of melphalan, prednisone, and thalidomide at the beginning of treatment, or should we save thalidomide for later treatment?

Dr. San Miguel: I think it is impossible to answer this question. The response rate with thalidomide plus dexamethasone as up-front treatment is not very impressive. It is similar to the response rate observed with this combination in refractory patients. This means that thalidomide has a completely different mechanism of action from chemotherapy. Therefore, patients who have received chemotherapy still have the option of treatment with thalidomide plus dexamethasone. I recently saw a patient who was exposed to VAD, autologous-transplant bortezomib, and thalidomide plus dexamethasone; had received a liver transplant; and had been treated with melphalan, but had never received melphalan at the low dose. He responded well after receiving the conventional melphalan-prednisone for the first time. The good news is that, depending on previous treatments, the use of alternative drugs can be of help.

Dr. Kyle: I would emphasize Dr. San Miguel's comment; we should not forget about melphalan and prednisone. They are both useful agents. Living with melphalan and prednisone for 40 years has been a frustrating experience, however. We are entering an era in which we have additional drugs, eg, thalidomide, bortezomib, lenalidomide, and others to come. The challenge will be to use these in conjunction with or without autologous stem cell transplant. I think it will take time to sort all of this out.

Dr. San Miguel: What is the panel's opinion about the toxicity of thalidomide?

Dr. Harousseau: The important point regarding toxicity is that the impact of side effects depends on the results. Patients who respond well are able to tolerate more side effects than if their response is poor. My first patient received 400 mg/d and had a complete remission. He developed severe peripheral neuropathy, but said, "Don't stop the treatment. I am in complete remission."

Because I perform transplants, I use very toxic drugs. We always consider the efficacy-to-toxicity ratio. The tolerability of thalidomide is much better now that we use 200 mg/d. Other drugs, such as bortezomib, have approximately the same side effect profiles, so maybe it is no longer a major issue.

Dr. Kyle: Another consideration is that toxicity with thalidomide varies substantially from patient to patient. Some patients tolerate it very well, but others taking even modest doses have side effects that cause them to refuse the drug.

As Dr. Harousseau mentioned, the efficacy-to-toxicity ratio is a critical factor. I once had a patient with multiple myeloma who had become refractory to everything and who required a blood transfusion every 10 days. His platelet count had fallen to 20,000 per microliter of blood. He was producing 17,000 mg of monoclonal light chain in his urine each day. We put him on thalidomide, and he went to Florida for the winter. He called me up after 3 to 4 months and said, "I have numbness and tingling of my feet." I told him to see his oncologist in Florida, and suggested that he would need to reduce the dosage of the drug or perhaps discontinue it. Incidentally, the patient no longer required transfusions, and his light chain had decreased from 17,000 to 700 mg/d. He said to me, "I'm not so sure you're right, Doctor. I would much rather have numb feet and be here." He made the decision to continue therapy despite the numb feet.

Dr. Boccadoro: I agree with Dr. Harousseau. We use 100 mg of thalidomide so the toxicity is manageable. But we presented data where between 20% and 40% of patients discontinued the treatment, not for major toxicity, but for other reasons. Even at the lowest dose, patients still discontinue treatment; so we have a lot of work to do in changing the way we conduct studies.

Dr. Joshua: In several studies reported here, thalidomide has had an effect on event-free survival, but this does not translate into improved overall survival. The major reason for this is that patients tend to receive the therapy later in the disease course, which makes it almost impossible to evaluate overall survival in a randomized study. How should we address this problem? Should we look at the impact of new therapy on the survival of the whole myeloma population with historical controls?

Dr. Harousseau: This is a good question. We had the same issue with autologous transplantation. Some patients who were given the conventional therapy received a salvage transplantation when relapse occurred, so it was difficult to show the differences in survival in some studies. One possibility would be a randomized study of early versus late treatment. In the next IFM study, we will try to evaluate early versus late lenalidomide therapy.

We will compare patients receiving placebo or thalidomide for maintenance treatment after autologous transplantation. Upon relapse, patients in both arms will receive thalidomide. We will try to schedule the treatment on first relapse, although, as you know, this is difficult.