Edward A. Stadtmauer, MD
Chief, Hematologic Malignancies
Abramson Cancer Center
University of Pennsylvania
Philadelphia, Pennsylvania

Next-Generation Proteasome Inhibitors, MRD and Genetic Plasma Cell Signatures

Hi, my name is Edward Stadtmauer. I am the Chief of Hematologic Malignancies at Abramson Cancer Center at the University of Pennsylvania. I am reporting to you live at ASCO 2016 in Chicago, Illinois, from the *Managing Myeloma* booth. Today, I am going to discuss a few brief highlights on some of the exciting advances in multiple myeloma and review some of the new data released here at ASCO. Once again, ASCO has been a great meeting for multiple myeloma.

The first abstract that I wanted to tell you about is entitled, “Genetic plasma cell signatures in high-risk smoldering myeloma versus multiple myeloma patients.” This is a study where the group that had done a study of carfilzomib, lenalidomide, and dexamethasone in newly diagnosed patients, showed near-complete remission in the newly diagnosed myeloma patients of 62% and the high-risk smoldering patients of 100%, and in fact 11 of 12 of the smoldering myeloma patients were minimal residual disease negative. So, that was a prior study. What this study showed was to look at the genetic sequence of the patients with newly diagnosed myeloma and smoldering myeloma and see if there was anything that could be discerned about prognosis or about responses. They did whole exome sequencing and RNA sequencing from baseline bone marrow samples of 39 patients with newly diagnosed multiple myeloma and 12 patients with high-risk smoldering myeloma. Interestingly, what they found was there was the same median number of mutations in the newly diagnosed or active myeloma patients as the smoldering myeloma patients. However, when they looked at what those mutations were, the mutations that were genes that are frequently seen in multiple myeloma patients were seen in 41% of the active myeloma patients, but none of the patients with smoldering myeloma. So, this study suggested that there is a difference to the mutations that are seen in the smoldering myeloma patients before they go on to active myeloma. And the clinical results suggested a very high response rate to the smoldering myeloma patients, higher response rates than in the active myeloma patients. So, the implications of this is, perhaps, if we treat patients before they develop these mutations, that they will have a higher response rate and a better outcome.

The next abstract that I wanted to talk to you about was called the “Clinical utility of the Revised International Staging System (RISS) in newly diagnosed multiple myeloma” patients. As you all know, a recent pooled analysis of 11 international trials formulated a new prognostic algorithm called the Revised International Staging System, or the RISS, for newly diagnosed patients with multiple myeloma. This is the same as the ISS system that we have used in the past except it adds to it high-risk chromosomal abnormalities, the deletion 17p, the 4;14 translocation, and the 14;16 translocation detected by the FISH analysis, as well as elevated LDH levels. This has been shown to be prognostically important. The difficulty with the RISS data is that it is only from patients who enrolled in clinical trials. So, the investigators for the Mayo Clinic wanted to see if they applied this system to a group of patients who are not on clinical trials, whether it would still have the same implications of outcome. So, they looked at 1900 patients in their practice who had a median followup of approximately 4.4 years, and they were looking for

overall survival and how it correlated with the ISS and the RISS systems. And what they found was that in the ISS system, about 30% of the patients were ISS stage 3, or high-risk patients, while in the new system, about 13.7% were of the high-risk nature. This actually correlates a lot more with our clinical observation that approximately 80% of patients with myeloma are of the standard-risk nature, and about 20% or less are of this high-risk nature. So, it does seem that this new system, the RISS system, is a better differentiator of multiple myeloma patients into these three survival subgroups. It is really important to identify who the patients are with high-risk disease, as this is the group of patients who have the poorest outcome with our standard therapies and are appropriate patients for novel therapies or for clinical trials.

The next study that I wanted to review for you was a phase 1 and 2 trial of the new oral proteasome inhibitor ixazomib, along with cyclophosphamide and dexamethasone for newly diagnosed multiple melanoma. So, in this trial, we know that the combination of bortezomib, cyclophosphamide, and dexamethasone is a very active regimen in multiple myeloma, and we also know that the combination of ixazomib plus lenalidomide and dexamethasone is a very active initial therapy. So the question is, is this combination of the oral proteasome inhibitor instead of the subcutaneous or IV proteasome inhibitor as initial therapy similarly good? So in this study, patients with newly diagnosed multiple myeloma were given the combination of ixazomib, which was given in what is the standard way, 4 mg on day 1, 8, and 15, along with dexamethasone 40 mg weekly day 1, 8, 15, and 22, and then cyclophosphamide, and the phase 1 part of the trial was either given as 300 mg/m^2 or 400 mg/m^2 day 1, 8, 15, and 22, and these were all given at 28-day cycles; 51 patients were accrued to this trial, 41 patients on the phase 2 part. In the end, it was felt that the 400 mg/m^2 was the appropriate phase 2 dosing, and in the end, better than 78% of the patients received better than a partial response, including a very good partial response of 33%, and two of the patients experienced a complete remission. The adverse events were relatively mild. The most common was cytopenias, fatigue, and GI side effects, which we have seen with this oral proteasome inhibitor. So of course, it is wonderful to see a number of all oral regimens for multiple myeloma. This allows our patients to be relieved of coming frequently to the clinical center for treatment, but before we can say that this is the optimal therapy, we will need to have some comparative trials of this approach with other approaches, and of course, there is the potential difficulty of the cost of oral agents.

The next abstract that I wanted to review for you was a report of the phase 1 and 2 style of carfilzomib, pomalidomide, and dexamethasone in patients with relapsed and refractory multiple myeloma. This comes from the MMRC consortium. As you know, Shah and others have reported on the combination of carfilzomib, pomalidomide, and dexamethasone, or as I call it CAR-POM-DEX, in the relapsed/refractory patients with very high response rates and good tolerability. This study particularly wanted to look at the less pretreated patients and particularly those who were refractory to immunomodulatory agents like lenalidomide. So, there were 55 patients who were enrolled in this trial. Patients were either lenalidomide refractory and were getting their treatment in second-line therapy, or were lenalidomide exposed and they could be in third-line or greater treatment. What they found in the phase 1 portion of the trial was that the third dose level, which was using 20 mg/m^2 of carfilzomib going to 27 mg/m^2 in the usual day 1, 2, 8, 9, 15, 16 fashion along with 4 mg of pomalidomide, was the dose-limiting or the maximally tolerated dose. The dose-limiting toxicities were all asymptomatic cytopenias. There was some fatigue, infection, and GI toxicities as the non-hematologic toxicities. In the end, this was a very active regimen. Greater than 76% of the patients had a greater than partial response within the first cycle of therapy, and even the patients who were lenalidomide refractory had a greater than

86% response, a greater than PR in that group of patients. The progression-free survival was 12.9 months with an overall survival at 18 months predicted to be 86%. So carfilzomib-pomalidomide-dexamethasone remains a very active combination in relapsed and refractory multiple melanoma, and now, in particular, the lenalidomide refractory group of patients.

The final abstract that I wanted to review for you was the use of PET-CAT scans as a good MRD marker in patients with multiple myeloma with a comparison and correlation with biochemical markers and flow cytometry. This is an important area because with the improving combination therapies that we have for myeloma and the increasing percentage of patients who are greater than VGPR and CR, it is becoming more and more important to differentiate the patients who are truly completely in remission versus those who still have a substantial amount of residual disease. This is what we called the MRD or minimal residual disease analysis. Traditionally, this analysis is done with a flow cytometry and can be very sensitive, but it does require a bone marrow aspirate and biopsy for assessment. So lately a PET-CAT scan, this imaging technique has been used for MRD analysis. So, this report is a single-center study where 72 patients were screened and 52 patients underwent PET-CT scan along with correlative biochemical evaluation and bone marrow examinations for residual disease. Unfortunately, only 11 patients in this 52 patient group did undergo flow cytometry for MRD. Interestingly, the PET-CT scan result had no relationship to the biochemical markers of SPEP, UPEP, etc., but there was very good agreement in that small group of patients between PET positivity after treatment and MRD positivity by flow cytometry. So, it would be wonderful, and we are always looking for a noninvasive approach to assessment of minimal residual disease, and it would be great if an imaging technique was such a technique that would have low toxicity and ease of use. And now that we have more and more patients who are clinically in complete remission, the MRD testing is becoming more and more important. Obviously, this study is interesting but requires larger groups of patients and does not yet validate that this is the way of determining minimal residual disease.

So, this is a review of five very interesting multiple myeloma abstracts at ASCO 2016. Thank you for joining me in this activity, and please stay tuned for more information and resources available at *ManagingMyeloma.com*.