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Novel Drugs, Conditioning Regimens, and Induction Therapy

Hi, my name is Dr. Joshua Richter. I am a Clinical Assistant Professor at Rutgers University, and a practicing hematologist/oncologist at the John Theurer Cancer Center in Hackensack, New Jersey. I specialize in plasma cell dyscrasias, more specifically, multiple myeloma. I am here reporting to you live from ASCO 2016 at the *Managing Myeloma* booth. I would like to talk about some of the exciting data that we have been presenting here at the current meeting.

The first trial I would like to talk about is the updated data from isatuximab in the setting of relapsed and refractory multiple myeloma. Isatuximab is an anti-CD38 monoclonal antibody, and we are here to present the updated data for the single-agent use. Combination studies are also being presented later in the meeting; however, the updated data from the phase 2 was presented yesterday. Basically, what we found is that the dosing of the drug at 10 mg/kg and above resulted in significant response rates in heavily pretreated groups of myeloma patients. These patients had a median of 5 prior lines of therapy, and in some cases up to 14 prior lines. We found that at the 10 mg/kg group, we found an overall response rate of 29%, and overall across all subgroups, we found an overall response rate of around 24%. This included patients who were heavily pretreated and were even quadruple refractory. So, patients who had already been not only exposed but refractory to the four key drugs, lenalidomide, carfilzomib, bortezomib, and pomalidomide, we still found a 20% response rate with the single agent. This gives hope to patients who otherwise have a grim prognosis based on their heavily refractory nature. Further studies are needed to find out the proper combinations that we can use this in managing our patients.

Another study I would like to talk about is the updated data from the phase 1 studies of plitidepsin. Plitidepsin actually comes from a sea squirt and relates to a eukaryotic elongation factor which is highly overexpressed in multiple myeloma cells. It turns out that by this mechanism we have found a brand new way that we can attack myeloma cells outside of the classical approaches using proteasome inhibition and immunomodulatory agents. As a single agent, we found that the response rates overall were approximately 56%. In general, the drug was well tolerated and had very a few nonhematologic toxicities. In relation to hematologic toxicities, it was very mild and actually quite manageable in a clinical practice.

Another study I would like to talk about is the updated phase 1/phase 2 data looking at two different trials trying to improve the results in the salvage transplant setting. The standard of care for salvage transplant and even upfront transplant across the years has been single-agent melphalan. Despite other combinations being use in other diseases such as lymphoma, combinations like BEAM and BEACOPP, in the realm of myeloma, nothing has proven better than single-agent high-dose melphalan. When engaging in salvage transplants where patients have already received one or more prior transplants, we have still only been able to use the

single-agent high-dose melphalan. In general, the expected duration of remission is about 40%-50% of what you receive from your first transplant. We are hoping to improve this with some of the synergy from the novel agents. In this study, we looked at two different combinations, one the addition of bortezomib to high-dose melphalan, and in the other the addition of thalidomide and bortezomib to melphalan in hopes of incurring some degree of synergy to lengthen the duration of disease control in the salvage setting. In the melphalan and bortezomib group, the overall response rate was around 44%, with a median progression-free survival of around 16 months, and median overall survival of around 60 months. The combination of bortezomib, melphalan, and thalidomide revealed an overall response rate of almost 70%, with a median progression-free survival of 9.3 months, and a median overall survival that has not yet been reached with a median follow-up of around 18 months. This data is extremely encouraging. In the realm where we have many new drugs approved, four new drugs approved in the last year and new drugs in the pipeline, we are always looking to improve our standard of care. Further study is needed to see whether or not the addition of these novel therapies to high-dose melphalan will lead to longer disease control in the salvage setting.

Another study I would like to talk about is the phase 1 data for venetoclax. Now, venetoclax is a potent BCL-2 inhibitor, and it turns out that venetoclax is highly active in certain patients with multiple myeloma, especially those who have a high expression of BCL-2, and specifically the 11;14 translocation. For years, we have been struggling to find therapies in myeloma that specifically target certain subpopulations. Instead of a one-size-fits-all, we are really looking to target certain patients that have specific, either demographic or cytogenetic abnormalities to find the ideal therapy that fits them. Here, we find venetoclax, an oral agent that specifically has activity in those patients with 11;14 translocation. In this study, the use of venetoclax yielded a 24% overall response rate, but there is more than just a response rate. Those patients, especially those with 11;14 translocation and high BCL-2 expression, had rapid and deep and durable responses. We may be on the verge of being able to identify specific therapies for specific subpopulations of patients with myeloma. Again, this is early data, phase 1 data, but we are hoping that with further study we may be able to find a specific therapy for each individual patient with multiple myeloma, and ultimately lead towards cure for the disease.

So, what about induction therapy? A big focus here in the myeloma community now has been looking at the relapsed/refractory setting, but what about the induction setting? Does it matter how you approach your patient when they first get diagnosed? Dating back to the VISTA trial, we have come to understand that proteasome inhibitor-based induction therapy, specifically bortezomib-based induction therapy, has been a cornerstone of managing myeloma in the upfront setting and has yielded long-term survival benefit. In fact, the updated data from the VISTA trial confirmed that after 5 and 6 years, those patients who received the bortezomib-containing regimen upfront maintained their overall survival benefit. Now, there are many ways to approach upfront therapy of bortezomib, VRd, CyBorD, bortezomib-dexamethasone, as well as purely IMiD-based, or immunomodulatory-based, induction therapies. In this trial, they really looked to sort out the data to see what was the best regimen, and that if you looked at, accounting for high-risk cytogenetic features, are you able to isolate what the optimal therapy is? Now when we looked across the board, it looked like with a first glance that CyBorD, bortezomib and dexamethasone, and VRd all had similar overall response rates and overall survivals. However, when multivariate analysis was undertaken, it turned out that the VRd regimen turned out to be superior. So, while upfront regimens are constantly in evolution, this kind of points us in a direction right now that if you are going to go with bortezomib-based

induction therapy, really it seems to be emerging that VRd seems to stand out above the crowd as the regimen of choice.
So, it is all well and good to talk about the use of all these drugs and clinical trials, but what about in a real-world setting? And what is really interesting this year has been a study looking at how proteasome inhibitor- and immunomodulatory-based therapy regimens are used in the real world. A large database was evaluated to see what were the characteristics of how these drugs would be utilized out in the community. So, we had patients receiving a purely IMiD-based relapsed setting regimen, a purely proteasome inhibitor-based relapse regimen, and those patients who received both in the relapsed setting. When the database was mined, there were certain factors and characteristics that came out for people who were treated with the combination of an IMiD and a proteasome inhibitor in the relapsed setting. It turns out that the patients who were treated with these regimens were younger, had commercial insurance, and tended to have a shorter duration of lengthy therapy for their first treatment. Again, what this really seems to bring about is that the general feeling of the oncology world as a whole, and specifically the myeloma world, is that patients who are younger and may have more aggressive disease, as indicated by their shorter initial duration of disease control, the approach seems to be treat them with multiple mechanisms of action, that it is not good enough to simply approach to them with an IMiD or proteasome, but the combination of both together really seems to be the approach that we have all taken. And this is something that we are seeing in all settings in myeloma, that if you can attack the cells from multiple lines, multiple approaches, the argument has always been triplet versus doublet, and now we see the triplet and the “holy trinity” of triplets at this time in myeloma is the proteosome inhibitor, the immunomodulatory agent, and the steroid. This combination really seems to be key in long-term disease control, especially for those patients that we feel may be at higher risk either to cytogenetic risk factors or short duration of remission from their initial therapy.

Now, what can we learn from patients as they relapse? Are all patients the same? Should they be treated the same? One interesting abstract looked at the role of elevated free light chains in the relapsed setting. So when we evaluate our patients, and in general we evaluate patient’s disease markers once every cycle, which again most cycles are either 3 to 4 weeks. We send a variety of lab tests including chemistries, complete blood counts, quantitative immunoglobulins, serum protein electrophoresis, and immunofixation, and very importantly a free light chain analysis. One of the things that we have come to understand is that there are multiple subclones within the myeloma genome within each patient, and you may have complete control of the total disease, and then you may see free light chain escape. So, there are patients that we see that have an M-spike that remains low and stable, and then all of a sudden have a free light chain that takes off, either kappa or lambda. Now, the question is, is this just food for thought or does this mean something from a prognostic standpoint? And what this study set off to do was look at patients who had particularly high levels of serum-free light chains, greater than 1000 mg/dL, and what this study looked at was patients who had this in the relapsed setting. Now, on the whole, patients who presented in the relapse with a serum-free light chain of greater than 1000 mg/dL had a median survival of around 5 months, which is quite dismal. Now, what this gives us food for thought is that if patients present in an aggressive physiologic way with visceral disease, obviously we attack the disease with a more aggressive regimen, triplets, even quadruplets in some settings. What has typically been the case is that people with more biochemical relapse or more indolent less visceral response may be able to be controlled with doublets. I think what this study brings up is that patients present, even if they do not have hypercalcemia, renal failure, or severe anemia, if they simply have a lab abnormality of high free

light chain, they may be someone that biologically has a tendency to have a poor outcome. These may be patients that you may want to strongly consider a triplet-based regimen, and again, triplets can be whatever you want. Classically, it is a proteasome inhibitor, an immunomodulatory agent, and a steroid. However, now especially at this year's ASCO we have seen emergence of other triplets with other mechanisms of actions with drugs such as histone deacetylase inhibitors as well as the monoclonal antibodies. But if you see a patient in your clinic that has a high free light chain, you may want to be more aggressive about trying to achieve rapid disease control and long-term disease control, and again, these may be a subset of patients that you may want to be more aggressive about considering clinical trials given their inherent poor prognosis.

I would like to thank you for joining me today, and please stay tuned for more information always available at *ManagingMyeloma.com*.