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Smoldering Myeloma, Outcomes Predictors and Checkpoint Inhibitors

Hi, my name is Bob Orlowski. I am the Director of the Myeloma Section at the University of Texas MD Anderson Cancer Center and also the acting chair of the Department of Lymphoma/ Myeloma, and I am reporting to you today live from ASCO 2016 which is in Chicago, Illinois, and I am presenting from the Multiple Myeloma booth of *Managing Myeloma*. There are a lot of exciting developments happening in myeloma at ASCO, and I am going to highlight just a few of the abstracts that I think are exciting and that hopefully will help you to manage your patients with myeloma and will also make myeloma patients more informed about their disease.

One of the areas that has seen a lot of changes in myeloma is the recent change in the definition of what is symptomatic myeloma. And as you know, now patients who have 60% or more plasma cells in the bone marrow, or an involved-to-uninvolved free light chain ratio of 100 or more, or have more than one focal bone lesion on MRI are treated as symptomatic myeloma. But there also are patients who are still right now considered high-risk smoldering who progress very rapidly, and one of the abstracts looked at the influence of changes in the monoclonal protein as well as changes in the hemoglobin, and what they found in this study is that patients who were diagnosed with smoldering myeloma who were high-risk and whose monoclonal protein rose within the first 6 months of diagnosis, or if their hemoglobin dropped, those were patients who were particularly at high risk and they were dubbed ultra-high risk, and these are patients that may in the future be redefined as having symptomatic myeloma, and therefore may require therapy. Therefore, I think if you have a newly diagnosed high-risk smoldering patient, you should definitely see them probably in the first 2 to 3 months and probably every 2 to 3 months initially just to make sure that you know the trajectory of their disease.

Another abstract focused on the role of minimal residual disease and the ability to achieve it in high-risk multiple myeloma. Now, there is a couple of ways that you can measure MRD. Of course, there are the blood tests and the urine tests for monoclonal protein, and you can also do things like a PET scan or an MRI, but probably even better is flow cytometry with immunophenotyping of the bone marrow, and it may be in the future the next-generation sequencing will be involved as well. So, high-risk patients are folks who have a very good response to treatment but unfortunately often relapse very quickly. What was found in the study of MRD is that patients who achieve MRD negativity do better than those who are MRD positive, and also if you achieve a stringent complete remission with maintenance therapy after induction and transplant for high-risk myeloma, you do better. So, I think that for now I would recommend that all patients after stem cell transplantation and also during maintenance undergo a bone marrow aspirate and biopsy with flow cytometry looking for MRD; in part, because those who are MRD negative, you can tell them that they will have a better outcome. We still have some holes in the data because we do not know what happens if we take MRD positive patients and if we treat them and they convert to MRD negative, will they have a better outcome than if we do

not treat them? I think, and many studies suggest that the answer is yes, but it is probably still too early to use the results of MRD testing to guide whether additional therapy is used or not. Another area that there was interest in is using biomarkers to try to determine whether patients will respond to therapy or not, hopefully earlier than things like measuring the monoclonal protein. And one abstract looked at the role of changes in the alkaline phosphatase as a predictor of outcome for patients being treated with ixazomib-based regimens. Ixazomib, of course, is the recently approved oral proteasome inhibitor and is an excellent drug in the relapsed and/or refractory setting. What was found is that a rise in the serum alkaline phosphatase was associated with a better chance of achieving at least a partial response after cycle 1, and the therapy particularly that was used was ixazomib with cyclophosphamide and dexamethasone. Just for historical background, you should know that alkaline phosphatase has been found in other studies to predict for a good outcome, both with bortezomib as well as with carfilzomib. I think that this would be useful to measure, especially after the first or second cycle, because sometimes patients with myeloma can take 1 or 2 or even 3 or 4 cycles before their monoclonal protein begins to drop, and if you see a rise in the alkaline phosphatase very early without a change in the monoclonal protein, that may give you further impetus to continue them on that treatment. So, this is another marker that hopefully you will be able to use in managing your patients better.

Another study looked at the preferences of prescribers for using new therapies, and this was actually based on a survey that looked at community practitioners who attended continuing education events and medical education seminars, and it looked at prescriber practices before the data about carfilzomib, lenalidomide, and dexamethasone were available, and also after carfilzomib, lenalidomide, and dexamethasone data were presented. As you probably know, there was a large study which showed that carfilzomib-lenalidomide-dexamethasone was superior to lenalidomide-dexamethasone for patients with 1 to 3 prior lines of therapy. And what this survey found is that after data did become available, the prescribing practices for community hematologists and oncologists changed quite a bit because they used less bortezomib, lenalidomide, and dexamethasone, and more carfilzomib-based regimens including carfilzomib-lenalidomide-dexamethasone as well as carfilzomib-pomalidomide-dexamethasone. So first of all, I think this validates the utility of these continuing education and medical education events, and also, I think this means you should take a bow and clap yourselves on the back because it means that all of you really are keeping up-to-date with all of the latest developments in the multiple myeloma field because people are taking up these new regimens very quickly and not waiting years to apply the best therapies to patients with myeloma. So, that is certainly very encouraging.

And then the last abstract that I will mention is one that is an oral presentation being given later in this meeting which is looking at the combination of lenalidomide and dexamethasone with pembrolizumab. Those of you who come to ASCO for the solid tumor part I am sure know about pembrolizumab. This is an antibody to a checkpoint protein called PD-1, and pembrolizumab has shown great clinical activity in a number of solid tumors as well as Hodgkin lymphoma. What we think is that what happens in patients with cancer is that their tumors suppress the immune system. Pembrolizumab is a drug that can, if you will, remove the brakes from the immune system and helps the immune system to fight the tumor better. So in this study, which predominantly focused on patients who had lenalidomide refractory disease, the study showed that combining pembrolizumab with lenalidomide-dexamethasone was able to achieve about a 40%-50% response rate, even in refractory patients. And I know a patient that I put on that

remember whose disease was progressing on lenalidomide and dexamethasone, and then just with the addition of pembrolizumab they started to have a nice response and ultimately entered a very good partial remission. So, these are really the first data that show that these checkpoint inhibitors are active in combination in multiple myeloma, and there are phase 3 studies that are coming to try to validate these further, both in combination with lenalidomide-dexamethasone and in combination with pomalidomide and dexamethasone.

So, thank you very much for tuning in, and I hope that this review has been helpful in your future and current management of patients with multiple myeloma.