Managing Myeloma

Efficacy of Venetoclax in Patients with RRMM

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Welcome to *Managing Myeloma.* My name is Shaji Kumar. I am a Consultant in Hematology at Mayo Clinic in Rochester, Minnesota. Today, I will be reviewing the results of the data that looked at the use of the venetoclax as a targeted therapy for relapsed and refractory multiple myeloma. As you know, patients with multiple myeloma continue to relapse despite all of the effective therapies that have become available over the past decade. As a result, we continue to need new therapies, especially those that are targeted toward the disease biology, in order to continue to improve the outcome of patients with myeloma. Venetoclax is a small molecule that is targeted to inhibit BCL2 proteins. Now, the BCL2 family of proteins plays a key role in myeloma cell survival, especially in the face of the multiple therapies that these patients receive.

In the preclinical studies, we noticed that BCL2 inhibition can result in myeloma cell death, and this led to development of phase 1/2 trials which looked at venetoclax in patients with relapsed and refractory multiple myeloma. In this phase 1 trial, we enrolled a total of 66 patients with relapsed multiple myeloma, with a median of five prior lines of therapy (some had as many as 14 prior lines). Patients received escalating doses of venetoclax during the phase 1 portion, and once we reached a phase 2 recommended dose, we moved on to a dose expansion phase which enrolled additional patients at the maximally tolerated dose. What we found in the study was, despite the significant prior therapies in these groups of patients, we found an overall response rate of 21%. When we specifically looked at the 30 patients who had a translocation 11;14, the overall response rate was 40%. Now, the reason why we specifically looked at the 11;14 translocated patients is based on the preclinical data suggesting that these patients may be exclusively sensitive to BCL2 inhibition. Here is the first instance where the preclinical observations have clearly translated into clinical results.

It is also very important when we look at the depth of response. Out of the 40% of patients with an 11;14 translocation who had a response, nearly two-thirds of these patients had a very good partial response or better. This is especially significant when we think about this group of patients; 75% of these patients had received a prior immunomodulatory drug or bortezomib or a transplant, and in fact, 67% of these patients were refractory to both an immunomodulatory drug (lenalidomide), as well as bortezomib, suggesting that this is a heavily pretreated group of patients. Despite this,

we were able to see deep responses to single-agent venetoclax, highlighting the efficacy of these drugs in a specific subcategory of patients with the translocation 11;14.

Based on the preclinical studies, we also have a sense of what the biology is underlying these 11;14 patients. Based on that, we did some additional biomarker studies in this clinical trial, especially looking at the ratio of the BCL-XL expression as well as the MCL1 expression. What we found was that in patients with the high BCL-XL expression and low MCL expression, the drug was even more efficacious. Out of the nine patients who had a favorable profile with the BCL-XL, eight patients actually responded to therapy, suggesting that we may be able to develop a biomarker-based strategy for utilizing this agent in patients with relapsed disease.

I think the key message from this clinical trial is venetoclax is an active agent, especially in patients with 11;14 translocation and particularly among those group of patients with a biomarker that suggests a profile with high BCL-XL and a low MCL1. Identification of biomarkers will have two roles. One, it will allow us to identify patients in whom single-agent therapy can be utilized. It will also give us a better sense of the biology of the disease so that it will allow us to study combinations that can overcome the resistance because of this unfavorable profile. Clearly, there are some challenges that are remaining. Right now, the next steps include getting a better sense of venetoclax alone, or particularly in combination with dexamethasone in patients with 11;14 translocation. Also, we are looking at combinations of venetoclax with both bortezomib as well as monoclonal antibodies and other proteosome inhibitors in the setting of relapsed disease. We also need to look at this drug in combination with the currently used triplets in patients with newly diagnosed myeloma. There is quite a bit of work that needs to be done, but the initial signals are very encouraging. Thank you for viewing this activity.