How is minimal residual disease (MRD) measured?

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

Hi, welcome to *Managing Myeloma*. My name is Edward Stadtmauer. I am a Professor of Medicine at the Abramson Cancer Center at the University of Pennsylvania in Philadelphia. I am frequently asked questions like, how is minimal residual disease defined and measured? This is an evolving area, but an area of great interest, particularly in clinical trials and defining endpoints of clinical trials, but it is ultimately to help determine the best therapy for our patients. Obviously, we have the standard clinical tests to determine whether a person is in remission, the tests of serum protein electrophoresis and light chain analysis, the urine testing, or PET-CT scans and other imaging modalities, MRI scans, and of course, sort of the gold standard which has been a bone marrow aspirate and biopsy looking for any evidence of residual disease. We are finding more and more that even patients who are in complete remission by all of these other techniques still have a minimal residual disease, and we are also finding that we can correlate very sensitive tests of minimal residual disease to outcomes to therapies.

The most commonly used and probably best established technique of looking for minimal residual disease in a multiple myeloma patient is by flow cytometry. There are groups throughout the United States and internationally attempting to standardize this approach. So far, it is not 100% standardized, but it does look like eight-color flow cytometry of a bone marrow aspirate can be the best way ─ so far ─ of looking for minimal residual disease. If you take a good sample aspirate and find that there is no evidence of the original clone of myeloma by this flow cytometry, then that would be called MRD negative, and those patients in a number of studies are having better outcomes, particularly with progression-free survival, than the patients who are MRD positive. There is a lot of interest in using PCR techniques and also next-generation sequencing, where you take the patient's myeloma cells and find a unique genetic sequence for them. Then you can use very sensitive techniques to look for minimal residual disease by looking for these sequences, and again, there have been some nice studies that correlate patients who are MRD negative by these gene sequencing techniques with having a better outcome than those who are positive, but ultimately, the best MRD test would be a test that does not require a bone marrow biopsy. It would be wonderful if we had a blood test that we could look for minimal residual disease or some imaging trial that would look for minimal residual disease. People have used MRIs and PET scans. People are looking at circulating DNA and seeing if that will correlate with better outcomes or worse outcomes. So far, you have to consider all of these techniques to be investigational.

So, as of this moment, certainly for clinical trials, it is very important to have some technique of minimal residual disease detection, and more and more, I think we are going to conduct clinical trials that are based on the MRD status as to whether you will receive a certain therapy or not receive a certain therapy. However, until those results of those studies are completed, I think we should consider the MRD testing interesting and reasonable to obtain, but of a clinically investigational manner.

Thank you very much and enjoy perusing the *Managing Myeloma* website.