Managing Myeloma

Guide to Challenging Cases in Relapsed/Refractory Multiple Myeloma: Improving Practice in 2017
Audience Participation Q&A

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At the conclusion of the symposium, the audience revisited a set of self-assessment questions they were asked at the beginning of the program. Below are the questions and responses, with explanations provided by the faculty.

Question #1

Dr. Orlowski: Mrs. Jones has been diagnosed with multiple myeloma, and she wants to know the stage of her disease. Her beta-2 microglobulin was 3.3 at the time of diagnosis, her albumin was 4.2, her lactate dehydrogenase was normal at 211, FISH analysis of the marrow aspirate showed a deletion of 17p. Also, radiographic studies showed multiple lytic lesions and her serum calcium was elevated at 11.0, but her creatinine was normal.

Based on these findings, her Revised International Staging System (R-ISS) stage would be:

1. I
2. II
3. III
4. IV

Dr. Voorhees: This is a patient who would have revised ISS II disease, because she has just one risk factor. Remember, to be staged as R-ISS III disease, you have to have ISS stage III disease based on beta-2, and either an elevated LDH or a high-risk cytogenetic abnormality. The important thing to realize is, the more high-risk features you accumulate – generally speaking – the worse you do.

Dr. Orlowski: It is a little bit of a trick question, by the way, because there is no stage IV (as in solid tumors and maybe lymphoma).

Question #2

Mr. Smith returns to your office with new bony pain, and you perform a bony survey showing that there is new lytic disease that had not been present before. Also, laboratory studies show that his monoclonal protein has increased from 2.0 g/dL to 3.0 g/dL, and he wants to know if he has relapsed myeloma, or myeloma that is both relapsed and refractory.

You tell him that refractory disease is often defined by any one of the following criteria EXCEPT:

1. The combination of new bony disease and increased monoclonal protein
2. Failure of myeloma to achieve better than stable disease on the recent therapy
3. Definite progression of myeloma while on the current chemotherapy combination
4. Definite progression of myeloma in less than 60 days since stopping the most recent therapy

Dr. Nooka: There are several definitions of refractory disease. It can be the failure to achieve better than a stable disease on the current therapy; or the progression of disease while on current therapy; or progression within 60 days after stopping therapy. The answer is #1. This is a tricky question because it is an “except” question, therefore it says that the combination of new bony lesions and increased monoclonal protein does not qualify for the definition of refractory disease.

Dr. Orlowski: New bony disease and an increased M-protein can be seen either in relapsed myeloma or in refractory myeloma. This sort of sounds like an academic exercise, but actually refractory myeloma is a worse actor than relapsed myeloma. It is important to know that the treatment options are different.

Question #3

Mrs. Jackson has been under your care for multiple myeloma, but is progressing on her initial combination therapy of bortezomib with cyclophosphamide and dexamethasone. After discussion of the various options, you jointly decide to switch to the regimen of daratumumab with lenalidomide and dexamethasone. However, she has chronic renal insufficiency, and you calculate that her creatinine clearance is 25 mL/min. based on a 24-hour urine collection, though she is not on dialysis.

Therefore, you decide to prescribe the following lenalidomide dose:

1. 25 mg p.o. on days 1-21 of every 28-day cycle
2. 10 mg p.o. on days 1-21 of every 28-day cycle
3. 15 mg p.o. every other day on days 1-21 of every 28-day cycle
4. 5 mg p.o. once daily

Dr. Voorhees: The answer is #3. This patient has a creatinine clearance of less than 30 mL per minute, but is not on dialysis. The dose of lenalidomide is 15 mg every other day on days #1 through #21 of a 28-day cycle, therefore the average dose per day is 7.5 mg.

Dr. Orlowski: Lenalidomide is eliminated and it metabolizes well through the kidneys, so you do not want to overdose these people because they will have much more cumulative myelosuppression.

Question #4

Mr. Cohen is undergoing second-line therapy with ixazomib, lenalidomide, and dexamethasone, and the ixazomib is being given at the standard dose of 4 mg p.o. on days 1, 8, and 15 of every 28-day cycle. During cycle 4 he reports grade 1 paresthesia in his feet but has no pain or loss of function, so you continue without a dose change and his symptoms resolve in the week off. Then, in cycle 5, his paresthesia and pain return and are worse, and he has trouble cooking meals for his disabled wife, making his neuropathy at a grade 2 level.

You therefore recommend that he:

1. Hold ixazomib until the pain resolves and then restart it at 4 mg
2. Hold ixazomib until the pain resolves and then restart it at 3 mg
3. Hold ixazomib until the pain resolves and then restart it at 2.3 mg
4. Discontinue ixazomib and continue just with lenalidomide and dexamethasone

Dr. Nooka: I think with ixazomib, in clinical practice, you can see the neuropathy. When that happens, how I decide on dose reduction versus no dose reduction is based on pain and loss of function. I would stop treatment until the pain resolves and start it at 1 dose level lower, or 3 mg. Answer #2 is correct because it is a one-dose level reduction (2.3 mg would be two dose reductions).

Question #5

A 67-year-old female originally presented with bony pain, was found to have multiple lytic lesions, and multiple myeloma was confirmed on a bone marrow aspirate and biopsy. She had good risk cytogenetics and FISH studies, and got induction therapy with carfilzomib, lenalidomide, and dexamethasone. Stem cells were then collected, and she underwent high-dose melphalan with autologous stem cell rescue, and a post-transplant bone marrow showed minimal residual disease (MRD)-negativity. As a result, she decided to not go on maintenance therapy, and was monitored closely for the next three years. At that point, she developed new bony disease and a rising paraprotein.

You suggest that the following second-line regimen has the highest overall response rate based on available phase III studies:

1. Elotuzumab with lenalidomide and dexamethasone
2. Daratumumab with lenalidomide and dexamethasone
3. Ixazomib with lenalidomide and dexamethasone
4. Carfilzomib with lenalidomide and dexamethasone

Dr. Voorhees: Answer #2 is absolutely correct. In the phase 3 POLLUX study of lenalidomide-dexamethasone with or without daratumumab, the overall response rate for the triplet was 93%. In the ASPIRE study of carfilzomib-lenalidomide-dexamethasone, it was 87%, so it also performed quite well. Lenalidomide-dexamethasone-daratumumab is the correct answer.

Dr. Orlowski: That does not necessarily mean that this is what you should use on *every* second-line patient. You should discuss with the patient and take into account all of the factors Dr. Voorhees described in his talk (past medical history, adverse events, biochemical vs clinical relapse/progression, standard- vs high-risk disease biology, treatment history), and it may be one of these other options that would be something you would decide for her.

Question #6

One of your patients, a 72-year-old male, is on the regimen of daratumumab, lenalidomide, and dexamethasone for second-line therapy of relapsed myeloma and has no prior history of transfusions, but some coronary artery disease. He has been doing well with treatment and is in his sixth cycle, but then is involved in a motor vehicle accident and ruptures his spleen. After urgent splenectomy, his complete blood count shows a hemoglobin of 8, and the surgical team wants to transfuse him because he has dyspnea. However, the blood bank calls you and says that the type and cross they received shows reactivity against every unit of blood they have tested so far, and they do not want to proceed without your approval.

You give them a number of options, but which of the following would NOT be one of them:

1. Call the Red Cross to get more units to evaluate
2. Check the patient's prior red blood cell genotyping
3. Treat the patient's plasma with soluble CD38
4. Treat the reagent red blood cells with dithiothreitol

Dr. Nooka: The correct answer is #1. As daratumumab binds to the CD38 on red cells on the IAT, it can be pan-reactive, so by bringing in more units, you are not going to get clarification. The other 3 options are certainly theoretical options that possibly can help. Having the phenotyping based on the genes prior to starting the daratumumab can certainly help with identifying the right units at a later time. Using soluble CD38 and DDT are equally better options.

Question #7

A 75-year-old female presented about three years ago with progressive fatigue, and after her primary care physician noted anemia (Hgb 8.2) and a paraprotein, sent her to you for a consult. Your evaluation included a bone marrow aspirate and biopsy that found myeloma with good risk cytogenetics. She was started on "VRd-lite" with bortezomib, lenalidomide, and dexamethasone, and after 7 cycles she achieved a CR, but she was not interested in a stem cell transplant and decided at that point to come off therapy. Two years later her disease has relapsed with worsening anemia and two bone lesions, and a repeat bone marrow shows 50% involvement with high c-Myc expression.

The patient would like to avoid having to come to the office as much as possible and wants an oral regimen, so you recommend:

1. Elotuzumab with lenalidomide and dexamethasone
2. Daratumumab with lenalidomide and dexamethasone
3. Ixazomib with lenalidomide and dexamethasone
4. Carfilzomib with lenalidomide and dexamethasone

Dr. Voorhees: Ixazomib is an oral proteasome inhibitor, so #3 is the correct answer. If anyone had any questions about the c-Myc expression (a little vignette in the question) as it turns out, c-Myc overexpression may actually be a predictive marker of response to the ixazomib-lenalidomide-dexamethasone combination that was an explorative correlative aspect of that particular study that deserves further testing.

Dr. Orlowski: For those of you who voted for carfilzomib-lenalidomide-dexamethasone, it is certainly a great combination and could be the right thing to do, but if the patient wants an all oral regimen, there is not yet an oral version of carfilzomib available.