

What are the major side effects associated with daratumumab in combination with bortezomib and dexamethasone, and the best ways to manage them?

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Welcome to *Managing Myeloma*. My name is Dr. Robert Orlowski, and I am the Director of the Myeloma Section and also the acting Chair of the Department of Lymphoma Myeloma at the University of Texas MD Anderson Cancer Center in sunny Houston, Texas. One of the questions that I have been asked more frequently of late is, "What are the major side effects associated with the use of the daratumumab in combination with bortezomib and dexamethasone, and what are the best ways to manage them?" This question is particularly relevant because we just earlier this month had FDA approval of the combination of daratumumab with bortezomib and dexamethasone. This was based on a large phase 3 trial which was published earlier this year in the *New England Journal of Medicine* which showed that the daratumumab, bortezomib, and dexamethasone combination improved the progression-free survival by more than 60%, compared with bortezomib and dexamethasone. In terms of the different side effects of the three-drug combination versus the two-drug combination, we need to always focus on infusion-related reactions with daratumumab, which can be seen with daratumumab either alone or in any combination. About 40-45% of patients, especially with the first dose, will have an infusion reaction. This can be manifested by symptoms such as a mild temperature or even a fever, chills, rash or itching, and they can also have problems such as shortness of breath or even bronchospasm. Most of these are prevented or at least reduced in severity by premedications, and the premedication regimen should be a standard of care. At MD Anderson, what we use is a corticosteroid along with diphenhydramine, an H1 receptor blocker, and an H2 receptor blocker, acetaminophen, and montelukast. With that combination, you can usually reduce infusion-related reactions down to a relatively low level with mostly grade 1 or 2 severity. If you do see a reaction nonetheless, what you need to do is usually stop the infusion of the drug, wait until the reaction goes away, and if it is a mild reaction you can restart at a slower level. On the other hand, if it is a more moderate-to-severe reaction, you may need to add additional corticosteroids as a premedication.

What are other adverse events that you can see with a three-drug combination? Let's start with hematologic abnormalities. You can have more thrombocytopenia with this combination. Usually what I do for that is transfuse platelets during the first and second cycles, with the thought that I am going to support the patient and that probably the thrombocytopenia is due to bone marrow involvement with myeloma rather than due to drug therapy. However, if the thrombocytopenia is later on (for example, at cycle 5 or cycle 6) and it is new, then you may need to think about reducing the dose of bortezomib a little bit, or maybe the dose of daratumumab, although in my practice I do not usually reduce daratumumab dosing. You also can see a little more neutropenia with daratumumab and bortezomib, and you can use filgrastim (Neupogen), for example. That is something that you can do in the week off, because the bortezomib is given in week 1 and week 2 but not in week 3. Therefore, one option is to give a couple of days of growth factor support during that week.

Other issues that you can run into include peripheral neuropathy, which overall is a little bit higher with daratumumab, bortezomib, and dexamethasone than it is with bortezomib and dexamethasone. Most of that neuropathy is grade 1 or 2, and there is no real difference in the risk of grade 3 or 4 neuropathy. You may need to think about, especially if there is grade 1 neuropathy with pain or grade 2, reducing the dose of bortezomib or certainly use symptom-directed agents like gabapentin or pregabalin (Neurontin or Lyrica). Also, topical agents can be very effective, for example topical lidocaine, and tricyclic antidepressants can in some cases be helpful for neuropathy. Infectious complications are notable as well; part of that may be due to the neutropenia. I do not routinely give antibacterial prophylaxis, but you should give either acyclovir or valacyclovir because of an increased risk of shingles. If you have a patient who has a prior history of pulmonary infections, an antibacterial antibiotic may be worthwhile, or even gamma globulin could be considered. Finally, you can have increased GI effects including diarrhea, and the standard antidiarrheals should be very effective. The combination of daratumumab with bortezomib and dexamethasone is one of the best in the relapsed and refractory setting.

Hopefully, these tips will be helpful in your management of patients, and thank you very much for reviewing this activity.