What are the major toxicities associated with daratumumab in combination with lenalidomide and dexamethasone, and the best ways to manage them?

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Welcome to *Managing Myeloma*. My name is Dr. Robert Orlowski. I am the Director of the Myeloma Section and the Interim Chair of the Department of Lymphoma and Myeloma at the University of Texas MD Anderson Cancer Center in sunny Houston, Texas. One of the questions that I am frequently asked these days is, "What are the major toxicities that are associated with the use of daratumumab in combination with lenalidomide and dexamethasone, and what are the best ways to manage them?"

This question is particularly important given the recent FDA approval of the daratumumab, lenalidomide, and dexamethasone regimen. This was based on a large phase 3 study just published in the *New England Journal of Medicine* showing that daratumumab, lenalidomide, and dexamethasone improved the progression-free survival compared to lenalidomide and dexamethasone by 60%, which is a very dramatic benefit. Because daratumumab is a monoclonal antibody, one of the main side effects you have to consider is the infusion-related reactions that can occur. As a result, there is a regimen that can be used as a premedication that can include intravenous corticosteroids as well as diphenhydramine, an H1 blocker, and also an H2 blocker, acetaminophen, and montelukast given together. With those, you can reduce the risk of infusion reactions down to about 40% to 45% of patients. Most of those are grade 1 or 2, which typically get better just with stopping the infusion for a little bit of time and then restarting it at a slower rate. If there is a more severe reaction, you can think about adding additional steroids and then restarting at a lower rate. What are other side effects to consider with daratumumab? Let's start with the hematologic space. With daratumumab, lenalidomide, and dexamethasone, there can be a little bit of a higher risk of neutropenia and also a higher risk of thrombocytopenia, and those of course would be managed differently. On the neutropenia side, one option that you can consider is growth factor support. For example, you can dose people with filgrastim (Neupgen) in the 1 week off of lenalidomide, because the lenalidomide is given 3 weeks on and 1 week off. In terms of thrombocytopenia, what I like to do, especially early on in the first or second cycle when often the thrombocytopenia is more related to the amount of disease burden in the bone marrow rather than to the drug therapy, I like to transfuse those patients and support them and continue with full dose and regularly scheduled therapy so that you can get the maximum benefit. If the thrombocytopenia develops later in the course, for example, cycles five or six or later, then I would consider reducing the dose of lenalidomide or possibly reducing the dose of daratumumab. Although, in my practice I have not found that to be necessary. Other side effects that you can see with daratumumab, lenalidomide, and dexamethasone – in part because of the greater risk of neutropenia – is a greater risk for infection. I do not routinely prophylax patients with antibiotics, but in some patients who have a history of previous frequent respiratory infections, that may be something to consider. Also, herpes zoster can be seen, and I put all of these patients either on acyclovir or valacyclovir. You also can have a slightly higher risk of diarrhea, and that can be managed with

the standard antidiarrheals that you are probably already used to using. Dyspnea in the pulmonary category is also something that needs to be monitored, but usually, it is fairly low level and grade 1 or 2, which is mild to moderate. Those are the major issues that you do need to watch out for. Most of the infusion reactions that we talked about at the beginning happen only with the first dose, and typically with the second and later doses, the infusion reactions are either completely gone or much more mild. Usually by the time of the third dose, you can give daratumumab in a smaller volume and over a more rapid pace. Briefly, although that is not part of the discussion here, there are some data at the current American Society of Hematology meeting about the potential use in the future of subcutaneous daratumumab, which seems to be associated with a lower risk of infusion-related reactions and the duration of the infusion seems to be shorter, so that may be another approach for the future. Thanks very much for viewing this activity, and I hope that it will be helpful in managing your patients getting daratumumab, lenalidomide, and dexamethasone therapy.