Managing Myeloma

**Does the addition of a fourth drug increase the overall side-effect burden of therapy?**

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Hello, and welcome to *Managing Myeloma*. I'm Dr. Muhamed Baljevic, and many of us are frequently asked: When do we add a fourth drug to the induction regimen, and does this increase the side-effect profile and burden of the treatment to our patients? What is the data that we have seen from the trials so far that can inform us more in this direction?

Certainly, we can say that from the available trial data so far—from CASSIOPEIA,[1] which looked at daratumumab-VTd versus VTd, as well as the phase 2 GRIFFIN trial,[2] which looked at daratumumab-VRd versus VRd—we can say that there is a slightly higher rate of hematologic adverse events that are associated with the quadruplet arms compared to the triplet arms. We are talking about higher rates of neutropenia, leukopenia, lymphopenia, thrombocytopenia, as well as anemia.

There have not been that many non-hematologic Grade 3 or 4 events that were more frequently noted in the quadruplets; perhaps only fatigue, which certainly can be expected to be present more with the quads rather than triplets. It is important to understand that there were also signals with upper respiratory tract infections, pneumonia, et cetera.

It would not be unreasonable to very closely follow the quad-treated patients and perhaps even consider giving some sort of antibacterial prophylaxis during the induction period to minimize and avoid pneumonias and the bacterial infections that can be seen, considering the higher frequency rates of neutropenia and reductions in the white cell counts.

As a closing thought for my community colleagues, I believe that it is fair to say that at this point in time, we are still in the process of learning how and when we really want to use quadruplet regimens, whether we need to use them in all comers, or whether they should be reserved preferentially, perhaps, in high-risk patients only. Providers are certainly free to use the dara-VTd and we in fact have been seeing an uptake of this regimen for patients that are being referred for AHSCT to academic centers, following the completion of induction therapy. However, this is truly a regimen that has been more studied and developed for the European practice patterns. We are eagerly awaiting the results of PERSEUS phase 3 trial[3] that is going to answer whether the addition of daratumumab to VRd - which remains the standard of care – improves the PFS.

It is also considered acceptable to use KRd as a frontline to induction in transplant-eligible patients. What we have learned from the ENDURANCE trial[4] however is that patients with baseline cardiopulmonary as well as renal comorbidities might not be best suited for this regimen and should preferentially receive the bortezomib/ lenalidomide/ dexamethasone as a choice of induction.

Conversely, any patients with significant baseline peripheral neuropathy (which is often seen in diabetic patients) would probably be better suited for KRd-based inductions, provided that the cardiopulmonary and renal comorbidities are not of concern. We certainly look forward to following the trial data results on dara-VRd as well as potentially dara-KRd and even isatuximab-KRd which will, down the line, hopefully help us understand how best to utilize quadruplet regimens in our clinics for newly diagnosed, transplant-eligible myeloma patients.

## References


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