Managing Myeloma

How does adding a fourth drug to a myeloma treatment regimen affect the side effect burden?

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Obviously, one of the biggest concerns that we have with quadruplets is the potential for toxicity. There's no question the efficacy is much better. If efficacy was the only metric that we went by, then the quadruplets would be preferred over the triplets, but we also know that adding a fourth drug to the mix does increase the risk of toxicity. Whether we look at the GRIFFIN trial,[1] ALCYONE trial,[2] or the CASSIOPEIA trial,[3] we do see a higher rate of hematological toxicity, and also higher rates of more grade 3 and grade 4 hematological toxicities with the use of the four-drug combination.

So, what would be the implications of a higher rate of toxicity? In the younger patients who are going to a stem cell transplant, using a four-drug combination for a limited period of time, like four months of their induction therapy, the impact overall might be limited, though data from CASSIOPEIA trial suggests that these patients may collect less stem cells compared to the patients that are induced with the three-drug combination.

Now, in the patients who are non-transplant patients, continuing on these triplets for longer term can also bring out cumulative toxicity, particularly cumulative hematological toxicity that might limit how long you really will be able to give these drugs for.
So, the trade-off is, if you use four drugs, induce more toxicity, are we more likely to end up discontinuing some of these drugs? While giving it as a three-drug combination, we may be able to sustain the therapy for longer periods of time. That is important question because we know, at least in the triplet setting, the longer duration of therapy certainly seems to be associated with better outcomes in some of the studies. So, many of them have been designed to do exactly that in terms of study design.

Now, with some of these newer drugs, we don't know what the long-term effects could be because some drug like the monoclonal antibodies have been used in the setting only starting more recently. We know there is some immunosuppression that goes with this class of drugs; both proteasome inhibitors and monoclonal antibodies do increase the risk of viral reactivation of herpes zoster, hepatitis B reactivation, hepatitis C reactivation, and so forth.

So that is something that needs to be kept in mind. We know that these patients get to be profoundly hypergammaglobulinemic, especially when they're getting these four-drug combinations, and what would be the impact of these kind of toxicities in the long term? While these toxicities could be of concern, by limiting the duration of therapy, still getting the same degree of benefit, the quadruplets might be able to overcome that disadvantage by giving patients a drug-free interval, which will allow the patients to reconstitute their immune system in a better manner, now that the disease is under better control.

References:

1. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood*. 2020;136(8):936-945.
2. Mateos M-V, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): A randomised, open-label, phase 3 trial. *Lancet*. 2020;395(10218):132-141.
3. Moreau P, Attal M, Hulin C. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): A randomised, open-label, phase 3 study. *Lancet*. 2019;394(10192):29-38.