Transcript Details

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Is There a Role for Novel BCMA-Directed Cellular Therapies in Early Relapsed Multiple Myeloma?

Announcer:
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Dr. Mikhael:
Hello, my name is Dr. Joseph Mikhael, and I'm going to be chatting with you today about the role of using novel BCMA-directed cellular therapies in earlier relapsed multiple myeloma.

I mean, we know it's present, that we're typically using CAR T-cell therapy, and even bispecifics, much later in the disease course, after patients have had at least 4 prior lines of therapy, but we are seeing emerging evidence to use this earlier. The first comes in the form of the KarMMa-3 study where we took ide-cel, which is now one of the approved regimens in myeloma as a CAR T-cell therapy, but now used it versus the standard of care in earlier disease in patients with 2 to 4 prior lines of therapy.

And in this study, quite impressively, we saw in the primary endpoint, a dramatic improvement in progression-free survival of 13.3 months with ide-cel versus only 4.4 months with the standard of care. And so this is something that is exciting in the myeloma communities, as we potentially can use these CAR T-cell therapies earlier on. This was of course driven by a significantly deeper response rate, you see here the difference in response rates of about 30%, meaning about 71% in those with ide-cel, and 41% in those with the standard regimen.

Now, this did come with some toxicity, of course, as we do see cytokine release syndrome, although primarily lower grade and neurotoxic events lower grade. Of interest, a subgroup within this study is important, I think, to recognize, which is those high-risk patients, where we typically see in those early relapse settings where they have a very negative outcome. And consistently, we saw the benefit of using ide-cel earlier in the disease course in these high-risk patients, whether they had a higher tumor burden, extramedullary disease, triple-class refractory disease early on, or just high-risk cytogenetics. In each of these contexts, we see the consistent benefits of using it ide-cel.

Well, similarly, studies have now been done with cilta-cel, the other CAR T-cell therapy that we have approved later in the disease course. And in this study, the CARTITUDE-4 study, we now went even a little bit earlier on 1 to 3 prior lines of therapy, comparing it to the standard of care, in this case, either PVd, pomalidomide/bortezomib/dex, or DPd, daratumumab/pomalidomide/dex. And again, we saw really quite impressive progression-free survival difference where in fact, the median progression-free survival hasn't even been reached yet, with the cilta-cel arm looking that it's likely going to be over 2 years, whereas it was just under 1 year in the standard of care arm at 11.8 months. This was also driven by a significant difference in response rate of about 85% with cilta-cel and about 67% In those patients receiving the standard of care.

And interestingly, and we saw this a little bit in the KarMMa study as well, that although we still of course continued to see cytokine release syndrome and patients that experienced neurotoxicity, it does seem to be less so than in the later stage disease. So not only are we seeing CAR T's potentially introduced earlier with great efficacy, but also reduced toxicity compared to what we see later in the

disease course.

And then just looking to the future with other now bispecific antibodies. Lots of different approaches are being looked at earlier in the disease course. For example, combining teclistamab now approved in late stage disease to be combined with daratumumab and lenalidomide earlier in the disease course in patients with 1 to 3 prior lines.

And in this MajesTEC-2 study, we do really see impressive response rates here of over 90% of patients responding with a generally very manageable cytokine release syndrome, with the majority of them being grade 1, and a smaller fraction grade 2, and in this case, no grade 3 CRS.

Other studies looking to the future adding teclistamab to other combinations like daratumumab versus investigators choice of DPd or DVd in 1 to 3 prior lines of therapy. Now, the of the MagnetisMM-5 study now using a newer bispecific antibody in the form of elranatamab as monotherapy and in combination with daratumumab in patients with an earlier stage disease.

So I think all of these are pointing to us in the direction that these great therapies that we use in late stage disease of CAR T-cell therapy and bispecifics can be used earlier in the disease course. And this matches our understanding of the biology. We would expect that patients would do better earlier on as T-cells are less beaten down by prior therapies. And so now we've proven both with ide-cel and cilta-cel that this can be used, and perhaps even in a less toxic manner, and very likely we'll be using this more fully in earlier lines of therapies.

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