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From Late-Line Rescue to Early-Line Option: The Potential for Bispecific Antibodies in Multiple Myeloma

Announcer:
Welcome to CE on ReachMD. This activity, titled **"From Late-Line Rescue to Early-Line Option: The Potential for Bispecific Antibodies in Multiple Myeloma"** is provided by Prova Education.

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Dr. Mateos:
Bispecific antibodies have reshaped the treatment landscape of relapsed/refractory multiple myeloma. Recent findings suggest a role of these drugs in earlier lines of therapy. Are you up to date on the latest clinical evidence?

This is CE on ReachMD, and I am Dr. María-Victoria Mateos.

Dr. Costa:
And I'm Dr. Luciano Costa.

Dr. Mateos:
Dr. Costa, what is the rationale to move bispecific monoclonal antibodies earlier in the treatment paradigm of multiple myeloma?

Dr. Costa:
That's an excellent point. Bispecific antibodies have shown some very exquisite activity in later-line disease. So it made all the sense to move this very active class of drugs to earlier lines where you have usually a lower burden, a lower kinetics kind of disease that is less genetically heterogeneous, and, most importantly, you have a more robust immune system. That would be fundamental for T cell engagement and ultimately elimination of the myeloma cells.

Dr. Mateos:
Thank you very much, Dr. Costa. Just to add something that I consider relevant, proteasome inhibitors and immunomodulatory drugs and, more recently, the anti-CD38 monoclonal antibodies are taking part of the first line of therapy.

So the movement of these bispecific monoclonal antibodies to earlier lines of therapy represented a switch to a different mechanism of action.

Dr. Costa:
Absolutely. Dr. Mateos, you recently presented results from the phase 3 MajesTEC-3 trial at the ASH annual meeting, which generated lots of excitement. Can you review the key findings from this study for us?

Dr. Mateos:
Yes, sure. MajesTEC-3 is a phase 3 clinical study in which teclistamab plus daratumumab, a synergistic immunotherapy combination, was compared with daratumumab in combination with either pomalidomide and dexamethasone or bortezomib and dexamethasone in

relapsed/refractory myeloma patients after 1 to 3 prior lines of therapy.

Just to remark, all patients were previously exposed to proteasome inhibitors. All patients were previously exposed to IMiDs, and over 80% of the patients were refractory to lenalidomide, and 5% of the patients were previously exposed to anti-CD38 monoclonal antibodies. Teclistamab plus daratumumab resulted in the greatest PFS treatment effect to date with a hazard ratio of 0.17 in comparison with the control arm. It was possible to visualize a plateau phase after 6 months, suggesting a potential for functional cure.

At 3 years, 83.4% of the patients in Tec-Dara remain alive from progression. And the median progression-free survival in the control arm was 18 months. And this benefit was sustained across all prespecified groups of patients, including patients with high-risk cytogenetic abnormalities, patients with extramedullary disease, and patients previously exposed to anti-CD38 monoclonal antibodies.

The benefit in PFS translated also into a longer overall survival with a significant benefit and a hazard ratio of 0.46. This benefit was also observed in terms of response rate, and 81.8% of the patients achieved complete response with Tec-Dara, and in the evaluable population, almost 90% were in MRD negative.

From the safety profile point of view, I would like to remark infections grade 3/4 were the most relevant adverse event reported in Tec-Dara, but especially during the first 6 months, then decline over time, and patients should be supported with infection prophylaxis, monitoring, and established immunoglobulin supplementation protocols. Cytokine release syndrome occured in approximately 60% of the patients, but it was grade 1, manageable, and resolved in all patients.

And another important consideration is the schedule of administration of teclistamab and daratumumab aligned with the Tec-Dara schedule, meaning that this is a convenient combination. It's steroid free from cycle 1, day 8, and also because of the subQ administration, it is possible to deliver this immunotherapy combination not only in academia but also in the community setting. Tec-Dara is a potential new standard of care for relapsed/refractory myeloma patients as soon as after 1 prior line of therapy. And based on this exciting data, the FDA applied a national priority voucher for this combination, and this means that a decision is expected basically in the upcoming months.

Dr. Costa:
Thanks, Dr. Mateos, this is an incredible summary.

I think it represents, really, a maturity age for bispecifics. For the most part, bispecific T cell engagers have been regarded as maybe a niche therapy; that is, essentially in academic centers and myeloma specialized centers for patients with very late disease.

But this changes everything. You have the highest possible level of evidence, the progression-free survival and overall survival, of an unprecedented effect size in patients as early as second-line therapy. So this goes from becoming niche therapy to become mainstream myeloma therapy.

The efficacy was a wonderful surprise for all of us. We all were optimistic about this combination, but the data turned out to be even better than we thought.

But perhaps the most surprising part was the safety.

What we saw here was essentially a rate of infection that is not substantially higher than patients just getting standard triplets. And with the mitigating strategies that you mentioned, that becomes essentially very safe and amenable to outpatient continuous long-term therapy.

Dr. Mateos:
Thank you very much, Dr. Costa. There are also recent data on bispecific monoclonal antibodies in newly diagnosed myeloma patients. What do our listeners need to know about these studies?

Dr. Costa:
That's a great point, Dr. Mateos. I think that's where our minds are right now. When we see something perform so well in relapse disease, the natural next step is to explore that in newly diagnosed myeloma. Of course we don't have yet large phase 3 data—that is coming—but the early evidence is very reassuring. For example, we have the MagnetisMM-6 trial, which is a trial with elranatamab, another BCMA directed bispecific T cell engager, in combination with lenalidomide and daratumumab in transplant-ineligible myeloma.

And what has been reported so far is response rate that is over 97%, and most of those responses are VGPR or better, with the safety profile that is acceptable with about 60% of patients with CRS, but all grade 1 and grade 2, very similar to what you show on MajesTEC-3.

We also saw at, at last ASH, the IFM2021-01 trial. So this is a single-arm study with teclistamab and daratumumab, essentially the same

combination that you explore on MajesTEC-3, in a patient population that is ineligible for transplant. Regardless of getting only 2 agents, the VGPR rate was 100%, and every single patient tested for MRD was MRD negative, and that was accomplished, again, with about 60% CRS, but again, no grade 3. And grade 3 or higher infection of 14%, which is not that dissimilar from conventional agents used this population.

We also saw recent data from the MajesTEC-4 trial, the safety run-in. So this is a trial that explored teclistamab with or without lenalidomide as part of post-transplant maintenance therapy. And again, was very well tolerated. CRS was 45% with no grade 3. And again, every single patient tested for MRD become MRD negative at 12 months.

We also saw, again, at last ASH, data from the phase 2 IMMUNOPLANT trial testing yet another BCMA bispecific called linvoseltamab, this time employed as consolidation therapy. Again, showing a very favorable safety and efficacy profile.

And all those responses seem to be very deep, so of course there's great excitement and great promise for deploying those agents as part of initial therapy, perhaps with some patients achieving a definitive disease response.

Dr. Mateos:
Yeah, definitely. I think that we are closer and closer to offer a potential cure for our patients with multiple myeloma.

For those just tuning in, you are listening to CE on ReachMD. I am Dr. María-Victoria Mateos, and here with me today is Dr. Luciano Costa. We are discussing the role of bispecific antibodies as early-line treatment for multiple myeloma.

Dr. Costa, what are some of the practical considerations for incorporating bispecific monoclonal antibodies into early-line treatment for patients with multiple myeloma?

Dr. Costa:
That's a great point, and I think some of our tasks in the upcoming years is to demystify a little bit the use of those therapies.

The challenges are essentially two: dealing with the CRS and then dealing with the risk of infection. I think what all our listeners need to understand is CRS is a problem for the first week, week and a half of administration of therapy, so essentially something seen during the step-up first target dose. Beyond that, it is not a problem. For most patients, CRS is grade 1. A smaller proportion of patients have grade 2 CRS, so those patients need to have access to corticosteroids, access to tocilizumab. And now there's a growing experience, particularly in the US, of administering tocilizumab even prophylactically. So patients can have the entire experience outpatient and becomes very rare that one of those patients has to be admitted, let alone becomes severely ill.

The second issue is the issue of infection. That's something that we, hematologists and oncologists, are much more comfortable with because really has been part of managing patients with myeloma forever. Of course the challenges here are somewhat unique, and the necessary mitigation strategies are also somewhat unique. And I think what has become clear in the last few years is the need to replace immunoglobulin with IVIG irrespective of level, because essentially all patients will become hypogammaglobulinemic when exposed to this class of therapy. So there are several guidelines in place, and the cornerstone is IVIG replacement, PJP prophylaxis, universal acyclovir prophylaxis, and very aggressive use of antimicrobials, particularly if patients become neutropenic. With those measures in place, the risk is very low, as we could see on MajesTEC-3, beyond implementation of those mitigating strategies.

Dr. Mateos, we are in an environment, fortunately, where we have had CAR T-cell available as early as second line for the last year or so.

So now, many of the physicians are facing this good challenge, which is to decide when to use a bispecific when you use a CAR T-cell therapy in their patients with early relapse and no prior BCMA directed therapy. How do you see that balance, and how do you make that choice?

Dr. Mateos:
Thanks, Dr. Costa, for the question. I think that the patient preferences are going to be something crucial and also the center in which the patient is receiving treatment, because if the center is an academic center with CAR T and bispecific monoclonal antibodies, maybe discussion with the medical doctor and personal opinions can influence. But if the patient is being treated in a nonacademic center, in a small center, if they want to receive CAR T, they have to be referred to another big center, whilst the bispecific monoclonal antibodies-based combination are going to be delivered in their center, and it is not necessary to be referred. So I think that this is also something very relevant, especially when we have a look to the efficacy and the safety data we've seen in MajesTEC-3, and this is one of the main advantages.

Dr. Costa:
I totally agree, Dr. Mateos. We usually think, and often present to patients or to our colleagues, proteasome inhibitors, IMiD, and anti-

CD38 monoclonal antibodies as being the 3 pillars of myeloma therapy. And I think we are crossing into the age where the bispecific T cell engagers become another one of those pillars, as very well exemplified by MajesTEC-3.

Dr. Mateos:
Okay. Thank you very much, and this has certainly been a great conversation. But before we wrap up, Dr. Costa, can you share your one take-home message with our audience?

Dr. Costa:
Yes. I think the take-home message is bispecific T-cell engagers are mainstream, safe outpatient therapy. They should be given high consideration in patients as early as on their first relapse. And it's up to us to become familiar and comfortable managing the little bit of inconvenience and administration and mitigating the toxicity.

Dr. Mateos:
I would like to share with the audience something similar. Bispecific monoclonal antibodies are off-the-shelf T cell-directed therapies, very effective in myeloma patients. They are moving to earlier lines of therapy. They are easily combinable, manageable, and broadly available in academic and in small centers. I personally consider that many patients will benefit from them.

And that's all the time we have today. So I wanted to thank our audience for listening in and thank you, Dr. Luciano Costa, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Costa:
Thanks, Dr. Mateos. It was great to share the microphone with you.

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