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Keeping Pace in Hematologic Malignancies: Newly Diagnosed Multiple Myeloma

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace in Hematologic Malignancies: Newly Diagnosed Multiple Myeloma” is provided by Prova Education.

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Dr. Hartley-Brown:
Significant progress has been made with induction therapy leading to longer and deeper remissions for patients with newly diagnosed multiple myeloma. So how do we decide which regimen is best? This is CME on ReachMD, and I am Dr. Monique Hartley-Brown.

Dr. Midha:
Hello. And I'm Dr. Shonali Midha.

Dr. Hartley-Brown:
So let's get started. Shonali, can you briefly review how we should be risk stratifying our patients, and which predictive biomarkers we should be on the lookout for?

Dr. Midha:
Sure. So as you know, we have several risk-stratifying systems, including Durie-Salmon, Revised-ISS, and, the revised-2-ISS. The majority of these, when looking at Revised-ISS and Revised-2-ISS do include cytogenetic factors such as IgH rearrangements and 17p deletions. However, the Revised-2-ISS actually takes out 14;16 translocations, as that affects PFS and not overall survival, but does include now, 1q, gain or amplification.

And another thing to keep in mind as we go forward is as we're looking at more targeted therapies is identifying those cytogenetic risk factors that will play into therapy in the long run.

Another factor that we can keep in mind is translocation 11;14, as we know is one of the predictive biomarkers for targeting with a BCL2 inhibitor. It is currently the only targetable drug in multiple myeloma based on the BELLINI trial, although there was a negative overall survival signal seen in the trial. When looking at just the translocation 11;14 patients, there was a progression-free and survival benefit seen and those patients treated with venetoclax, which is a BCL2 inhibitor.

So I think we'll be seeing that change over time moving towards cytogenetic or you know, molecular features defining myeloma more specifically, as we approach more targeted therapies in the future.

So turning now to guideline-recommended agents, it really is an exciting time for new therapies. Monique, what are the latest data showing us for transplant eligible patients?

Dr. Hartley-Brown:
That's a great question. The goal really for all patients is to achieve a very deep and sustained response. And there are many clinical

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trials that are looking at this. The FORTE trial is one pivotal phase 2 trial that looked at a carfilzomib-based regimen with transplant. The caveat was do we need that transplant? Do we need to look at carfilzomib with another partner? And really, the essence of that trial showed us that the outcomes for patients is still better for those patients to obtain transplant if they're eligible. And so we keep the transplant for those transplant eligible patients that are newly diagnosed. But more importantly, what we also saw is the depth of response is extremely important. And so, the FORTE trial kind of queued in the fact that the measurable residual disease status makes a difference. So the depth of response makes a difference, those patients' outcomes are better, their progression-free survival, overall survival is better.

The GRIFFIN trial has shown similar information, also a phase 2 trial. This particular one looks at a quad, which includes daratumumab added to lenalidomide, bortezomib and dexamethasone versus the triplet of lenalidomide, bortezomib, and dexamethasone alone. And again, the patients were transplant eligible patients and so they moved on to transplant, and on the back end received, you know, maintenance therapy different in both arms. And I won't go in depth about that. But the reality is the daratumumab-containing quadruplet arm showed better MRD rates and better outcomes for those patients. So we still have data that's coming out from the GRIFFIN study. But the two-year information is really pivotal.

And so, for that reason, we have other trials that are looking at MRD status. The MASTER trial we have some early data from the German trial GMMGHD7, that has shown that within 18 weeks of induction with isatuximab, len, bortezomib, and dex, we have a better outcome for patients with MRD status 50% versus about 35% or 36%. And so that really is really key.

Now the other question and the other factors to consider when selecting patients is who would be the ideal patient to receive a triplet versus a quadruplet? And that is something that we're still working on. And studies are looking at that for outcomes for our patients. And so, there's more yet to come with that.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Monique Hartley-Brown. And here with me today is Dr. Shonali Midha. Together, we're discussing emerging data for newly diagnosed multiple myeloma, and what that means for your clinical practice.

Shonali, what's new in terms of maintenance therapy for patients after autologous stem cell transplantation?

Dr. Midha:
Thank you, Monique. In regards to maintenance therapy after a stem cell transplant, what we've typically done per prior trials was single-agent maintenance with an IMiD, most commonly lenalidomide. However, as we approach patients looking at risk factors, specifically cytogenetic risk factors, there has been growing interest in attempting to achieve better outcomes with combination therapies and maintenance therapy.

One of the trials that looks into this is SWOG 1211, looking at the use of RVD plus or minus elotuzumab continued into the maintenance setting. And that patient population did include within their high-risk setting, primary plasma cell leukemia, patients with 17p deletions, IgH rearrangements, or 1q amplification or gain. And what's interesting there is, although there was no difference seen with or without elotuzumab, there are improved outcomes in regards to survival – progression-free survival, specifically, with combination PI, or proteasome inhibitor, as well as IMiD maintenance therapy.

Obviously, we do have to keep in mind the toxicities when seen in combination, the risk of neuropathy with certain proteasome inhibitors such as bortezomib or ixazomib, and as well as the added result on quality of life as it does require patients to come into the clinic for infusional-based therapies as opposed to just taking oral.

Similarly, if we look at the ENDURANCE trial that was comparing carfilzomib, Revlimid, dexamethasone versus the typical Velcade, Revlimid, and dexamethasone, and again similarly, although there was no difference seen between the two groups, there are added benefits to using combination PI and IMiD-based regimens for maintenance, especially in those high-risk groups.

Moving forward, with the addition of CD38 antibody as to induction therapies, we're now seeing the role of anti-CD38 antibodies, specifically daratumumab or isatuximab in maintenance regimens. So, one of these includes GRIFFIN, which did look at daratumumab used for an additional 24 months along with Revlimid in the maintenance setting. And then along with the ongoing trials of the maintenance phase of the trials of CASSIOPEIA and ALCYONE, which again are looking at the role of anti-CD38, either for a fixed or more prolonged duration in the maintenance setting.

The data from these are still coming out. However, with GRIFFIN, you can see at the two-year mark, a slight divergence of the progression-free survival curve. So, we hope that we'll see more data in the future.

So now let's turn our attention to transplant ineligible patients. What options can we provide for these patients? And how do you go about selecting these regimens?

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Dr. Hartley-Brown:
Another good question. Our patients for the most part, are diagnosed around the age of 70. And so we have an enormous amount of our patient population that are older than 70. And their quality of life is their most important concern. So how do we address these concerns for these patients? We have to think about what regimen we're going to give the patient and what the outcomes are going to be. And of the regimens that we know, there's been enough data that has been studied already in clinical trials to tell us that a triplet regimen should be the treatment for any patient, whether they're transplant eligible or transplant ineligible. Some of the triplet regimens that our transplant ineligible patients have been known to do well with, and consists of lenalidomide, bortezomib, and dexamethasone. Now, the steroid portion of it is very difficult sometimes. And so if you're thinking about an older patient over the age of 75, sometimes it would be better to reduce the steroid dose for those patients and consider an RVD light type of a regimen.

The MAIA trial has shown us that adding in, you know the anti-CD38 monoclonal antibody of daratumumab in place of bortezomib and doing the DRD regimen has been well tolerated for our patients over the age of 75. And they have better outcomes. So as soon as you can get these patients into a very deep response with a nice, tolerable regimen, their quality of life becomes better. And what do I mean by a nice response or an adequate response? I mean, getting their protein levels that are measurable down by at least 90%. So, you want to see an early response within the first few months, maybe between 4 and 6 months, getting a VGPR. And that is key. That is going to be very helpful. Considerations are also around the administration. Our patients that are older, they don't want to be stuck in the doctor's office all the time. They don't want to feel sick, they don't want to have to limit their livelihood and their retirement. I mean, lots of these patients are still very active individuals. And so how do we bridge that? We bridge it by allowing them to consider other options, oral regimens. We have ixazomib, and lenalidomide is an oral regimen. The daratumumab at a certain point becomes once a month. So all of these things are key to consider when discussing treatment for these patients.

Well, this has certainly been a fascinating conversation. Before we go, Shonali, what is your one take-home message for our listeners today?

Dr. Midha:
Thank you, Monique. And I think you really hit the nail on the head, when you said we have to think about quality of life in our patients. And I think going forward, we want clinicians to more heavily consider cytogenetic risk factors, things like deletion 17p, gain 1q, translocation 11;14, as well as, the typical-high risk IgH rearrangements when considering therapy in the induction and the initial treatment phase of myeloma. And moving forward, as targeted therapies become more available, understanding the role of targeted therapies in relation to these predictive cytogenetic risk factors that can be identified either by FISH or more sensitive methods in the future.

Dr. Hartley-Brown:
And I'll add, there's lots of new data for newly diagnosed multiple myeloma patients, including having the monoclonal antibodies upfront. Think about MRD status, the depth of response matters. Think about talking to your patients about route of administration of treatments. These are all key points that are necessary to think about. There's lots more coming, so stay tuned. Multiple myeloma, a cure is yet to come.

So, unfortunately, that's all the time we have today. And I'd like to thank our audience for listening in. Thank you, Dr. Shonali Midha, for joining me. It was a pleasure speaking with you today.

Dr. Midha:
Thanks. It was a pleasure to be here.

Announcer:
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