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Expert Insights on Multiple Myeloma Recognition & the Treatment Landscape

Announcer:
You're listening to *Project Oncology* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the multiple myeloma treatment landscape and therapies on the horizon is Dr. Samer Al Hadidi. He's an Assistant Professor in the Department of Internal Medicine in the Hematology and Oncology Division at the University of Arkansas for Medical Sciences. Dr. Al Hadidi, thanks for being here today.

Dr. Hadidi:
Thank you for having me.

Dr. Turck:
Well, to get us started, Dr. Hadidi, would you give us a brief overview of the current treatments available for multiple myeloma patients?

Dr. Hadidi:
Sure. We have multiple treatment options currently available for patients with multiple myeloma. This includes immunomodulatory drugs, things like thalidomide, lenalidomide, or pomalidomide; proteasome inhibitors, things like bortezomib or carfilzomib; steroids like dexamethasone or prednisone; and also, antibody drug targeting, CD38 drugs like daratumumab or isatuximab. We also have the chemotherapy agents, including alkylating agents, such as melphalan, followed by stem cell rescue or transplant. Also, the conventional chemotherapy that includes other chemotherapeutic treatments we use for other cancers, and also, active in multiple myeloma, such as alkylating agents like cyclophosphamide, for example. We also in a new era of treatments, we have the B cell maturation antigen targeted agents, such as the chimeric antigen, T-cell therapy, or CAR T-cell therapy. Those include ide-cel and cilta-cel, both of them were approved by the FDA to use. And also, the bispecific antibodies. And one approved product is called teclistamab, which target BCMA.

Now also, we have other treatment options likely nowadays with limited use given the other excellent activity of other agents we just discussed. And that includes other antibodies targeting a signaling lymphocytic activation molecule or SLAMF7, a drug called elotuzumab, and another inhibitor for the nuclear export called selinexor.

So in general, we do actually combination treatment when we treat multiple myeloma, and that includes more than one agent from different classes. Sometimes that includes three or four drugs. And that is different across valuable regimens we use and frontline setting or relapsed/refractory setting.

Dr. Turck:
And what challenges have been associated with some of the therapies you've mentioned?

Dr. Hadidi:
Yeah, there are multiple challenges that we deal with in clinic, and that includes that those treatments don't work for all patients in the same way. A subset of patients don't actually respond as well. And they don't have long responses, they don't keep their good responses. And also, those agents are associated with some side effects that are specific to the actual drug given. For example, bortezomib can cause a neuropathy, while carfilzomib can cause some cardiac adverse event, and that makes a patient-specific decision to decide on what to use according to patient's medical problems and adverse events from previous medical history.

Also, with those newly approved treatments, we have limited centers that can offer those treatments, including CAR T-cell therapy, and also, bispecific therapies, which were most recently approved. And that has to do with multiple issues, including logistics and such as lodging, for example, traveling, and other things that patients need to do to get those therapies.

Those also newer therapies, including CAR T-cell therapy and bispecific antibodies, are associated with specific side effects that include cytokine release syndrome, for example, and infections that will need appropriate attention and management.

Also, we have a problem in using treatments for myeloma as a continuous fashion. Many of our treatments are actually given until progression. And for patients, that could be inconvenient because that means lifelong treatment, and may result in issues with quality of life, for example.

And I think the last thing is that within all the data we have limited studies comparing those regimens together. So we know that those work in certain scenarios. But given that we have multiple drugs in the same class, we don't have enough data to compare those drugs in the same class together given they seem to be working in a similar way. So we don't know actually if some of those drugs are better than the others, if any, or both are equivalent.

Dr. Turck:
Now how could some of the more novel treatment options out there help address some of the challenges you mentioned in the multiple myeloma treatment paradigm?

Dr. Hadidi:
Yeah, we're excited to see the earlier results of new treatment options in myeloma. And that includes the bispecific antibodies and CAR T-cell therapy. And the earlier studies, those agents were used in heavily pretreated patients, and they resulted in really good response rates. This was double what we used to see with the older classes of drugs. So the hope is that we use such better therapies with better responses. And we can see that reflected in improved outcomes that matter for patients like living longer or living better. And this is ongoing and an open question to better understand.

I personally believe that we need to implement such new treatment modalities in what's called high-risk multiple myeloma, since we know that we did not improve much in that subset of patients. And most of the improvement we achieved was in the standard-risk patients. For example, we have patients with extramedullary disease or high-risk cytogenetics who should be the focus of our developments and earlier use of those treatment options, which are exciting.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Samer Al Hadidi about the current and future treatment options for multiple myeloma.

So, Dr. Al Hadidi, let's zero in on one type of novel therapy for multiple myeloma you mentioned. What more can you tell us about BCMA bispecific antibody therapy?

Dr. Hadidi:
Yeah, thank you for that question. BCMA, or B cell maturation antigen, is actually a cell surface protein that is expressed on the plasma cells, and that is a member of the tumor necrosis factor receptor family, and it's usually expressed in mature B lymphocytes and overexpressed in those plasma cells, and its activation actually leads to survival of plasma cells. So those BCMA bispecific antibodies are new treatment modalities that target CD3, which is present on the surface of T lymphocytes, and tumor-specific antigen. In this case, it's BCMA.

The good thing about bispecific therapy is they're available off the shelf to use for patients.

There are currently multiple CD3/BCMA-targeted bispecific antibodies in clinical development with promising early results in advanced myeloma.

Dr. Turck:
With that information in mind, what are some key findings from clinical trials involving BCMA bispecific antibody therapy?

Dr. Hadidi:
We have the only approved BCMA therapy so far, called teclistamab, was supported by study development called MajesTEC study, and that actually reported data on 165 patients who were triple class exposed. Those are patients who at least got one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 antibody-based therapy. And they were treated with weekly subcutaneous injection of teclistamab at a dose of 1.5 milligrams per kilogram, and around two-thirds of those patients achieved a response with a median duration of response of approximately 1.5 years. And those responses were good and included some complete responses around 40

percent of patients. And actually, one-fourth of patients achieved really deep responses with minimal residual disease negativity.

Those treatments were associated with significant toxicities that are relatively new in the field of myeloma and include things like cytokine release syndrome and immune effector cell-associated neurologic toxicities. And those were reported in around 72 percent for CRS and around 15 percent of patients for neurological toxicities, but most of those were grade one and two adverse events, which tend to be not as significant as grades three or four in general. Though also, we noticed that around three-fourths of patients developed some sort of infection, and around half of the patients developed significant infection. And since those studies were done in the era of COVID, a few patients actually died because of COVID. And those were up to seven percent in this specific study.

And there are other studies that looked into BCMA bispecifics and antibodies, and those showed early promising results similar to the teclistamab, and we're waiting for the full data on those agents.

Dr. Turck:
And as we close our discussion, Dr. Al Hadidi, do you have any final takeaways you'd like to leave with our audience today?

Dr. Hadidi:
The future of drug development in myeloma seems actually bright. And with the introduction of these novel immunotherapies and the potential to move them to earlier lines and do a combination therapies, I think we should be optimistic that we will get better results. And also, we should be careful because there is a risk of infection. We can see in earlier studies of combination therapies that we need to be aware of and address. And we should also try to focus development for patients in most need. And those include patients with high-risk multiple myeloma, plasma cell leukemia, and patients with extramedullary disease.

With the improvement we see on patient outcomes, we also need to focus our efforts to follow those patients for a longer period of time to better understand their outcomes. And finally, I think we should focus on improving quality of life for our patients and try to provide more tolerable treatment approaches that are limited in duration, especially for elderly patients who tend to have other comorbidities we should be aware of.

Dr. Turck:
Well, with those key insights in mind, I want to thank my guest, Dr. Samer Al Hadidi, for joining me to discuss how novel options, like BCMA bispecific antibody therapy, may impact the multiple myeloma treatment landscape. Dr. Al Hadidi, it was great having you on the program.

Dr. Hadidi:
Great talking to you. Thank you so much.

Announcer:
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