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Understanding the Advances and Current Challenges in RRMM Therapy

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Dr. Rahul Banerjee, MD, FACP has received compensation from the US Medical Affairs Department of AbbVie Inc. to prepare and present the following information and is speaking on behalf of AbbVie. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to ReachMD. I'm Dr. Charles Turck, and today, we'll be discussing the impact of novel immunotherapies on relapsed and refractory multiple myeloma care. We'll also examine how we can address unmet needs and challenges to improve the patient journey and clinical outcomes.

Joining me is Dr. Rahul Banerjee, who's an Assistant Professor in the Clinical Research Division at the Fred Hutchinson Cancer Center in Seattle, Washington.

Dr. Banerjee, it's great to have you with us.

Dr. Banerjee:
Thanks Dr. Turck. It's a pleasure to be here.

Dr. Turck:
Well, let's dive right in, Dr. Banerjee. What difficulties do patients with relapsed and refractory multiple myeloma face throughout their treatment journey?

Dr. Banerjee:
That's such an important topic. And to start, I'll share some background on the disease. Multiple myeloma is the second most common blood cancer in the US,[1] with approximately 36,000 diagnoses per year—so that's about 100 diagnoses per day.[2] It's actually the most common blood cancer in African Americans, making it a major source of cost disparities.[3] Patients diagnosed at 65 years of age or younger typically have a life expectancy exceeding ten years, whereas those diagnosed over 65 historically have had an expectancy of about four to six years.[4] Thankfully, outcomes have continued to improve, even in older adults with myeloma. However, without a curative therapy, these patients still encounter significant challenges, including treatment resistance and relapse.[5–7] By the time we get to later lines of treatment, survival rates decline, and this is largely due to complications from myeloma or its treatment, which lead to patient attrition.[2,8,9]

Complicating this even further is the fact that patients typically require multiple lines of therapy using different mechanisms of action. My patients often undergo numerous treatment regimen. Some of them have even received ten or more lines of therapy.[8–10]

In fact, with the adoption of combination therapy in earlier lines, most patients nowadays are exposed to the major treatment classes earlier in their care journey. As a result, patients become triple-class-exposed, and some patients may develop triple-class-refractory

disease.[11,12] These three classes typically include proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies.[13,14]

Nowadays, quadruplet therapy, which includes these three classes, has become the standard of care for newly diagnosed patients with transplant-eligible multiple myeloma.[14] That means, by definition, that these patients are often triple-class-exposed within about a month of diagnosis as they start treatment.[8] Based on data presented in the last year, quadruple therapy has become the standard of care for many transplant-ineligible patients as well.[15–17] The challenge, of course, is that triple-class-exposed patients historically have worse survival outcomes thereafter. This emphasizes the need for novel treatments that are specifically designed with these patients in mind.[11,12]

Dr. Turck:
So given that critical need, Dr. Banerjee, what novel therapies are helping to address the challenges faced by triple-class-exposed patients?

Dr. Banerjee:
Great question. So many of these new treatments are immunotherapies that rely on T-cell redirection to eliminate myeloma cells. Their continued development had led to the introduction of chimeric antigen receptor T-cell, or CAR T, therapy, as well as bispecific antibody therapy. These two classes of T-cell re-directing immunotherapies generally target B-cell maturation antigen, or BCMA, and have been studied extensively, really, primarily in triple-class-exposed patients.[18,19] There are other myeloma cell targets as well that can be utilized, for example, GPRC5D, but for this talk, we'll focus on BCMA.[20]

Now if we take a quick look at each of their mechanisms, CAR T therapy for multiple myeloma involves re-engineering a patient's T-cells to target BCMA on plasma cells. On the other hand, BCMA-targeted bispecific antibodies, which I'll refer to as BCMA bispecifics for short, uses engineered proteins to bridge native T-cells with plasma cells expressing BCMA. Ultimately, both approaches activate T-cells to destroy these plasma cells.[21]

But it's important to note that these immunotherapies leverage BCMA expression on multiple myeloma cells, but they cannot differentiate between normal and malignant plasma cells. As a result, patients on these therapies become immunocompromised.[21–23]

Dr. Turck:
That's a great overview; thank you. Now, can we talk a bit more about how BCMA-targeted CAR T and bispecific therapies differ when it comes to safety and dosing considerations?

Dr. Banerjee:
Absolutely. The risk of infection is higher with BCMA bispecifics than with BCMA CAR T, and that may be related to repeated plasma cell depletion following each administered dose of the BCMA bispecific.[24,25] Other factors may contribute to immunosuppression in this setting as well, including T-cells that become 'distracted' by the redirection process, and that reduces their ability to effectively respond to other infectious threats.[25,26]

And so, while BCMA-targeted CAR T and bispecific therapies demonstrate effective response rates and long-term durations of response, they do come with important safety considerations.[18,19,27–30]

For example, in addition to the increased risk of infections that I alluded to, both therapies may trigger cytokine release syndrome, CRS, as well as immune effector cell-associated neurotoxicity syndrome, or ICANS. However, these neurotoxicities are generally grades 1 to 2 with both classes of therapy, and ICANS is less common with bispecifics than with CAR T cell therapy.[18,19,27,29–31] There are important differences in treatment administration between the two types of therapy. CAR T therapy offers the advantage of a single intravenous infusion after lymphodepletion without the need for subsequent myeloma-directed therapy.[27,29–31] This is a driver of the quality-of-life benefit reported by patients in randomized trials of CAR T versus non-BCMA targeted options.[32,33]

However, the complete administration process for CAR T can still take 2 to 4 months. That includes initial referral, T-cell collection, bridging therapy during the manufacturing interval, CAR T infusion, and post-CAR T monitoring. Some patients are even hospitalized prophylactically during CAR T infusion to monitor and manage these potential adverse effects, for example, CRS.[1,27,31,34]

As for BCMA bispecifics, the time to get patients started on treatment can vary.[35,36] Most BCMA bispecifics are administered by subcutaneous injection, starting with a week of multiple step-up dosing. Step-up dosing entails gradually increasing the dose rather than starting with the full dose. This aims to reduce the risk of CRS. Once patients are shown to be able to tolerate the full bispecific antibody dose, they typically receive weekly treatment until they achieve and maintain the required response, which varies based on the BCMA

bispecific. Afterwards, treatment frequency is reduced to every two weeks per the package inserts, until disease progression or unacceptable toxicity occurs.[19,29,30]

But I just want to reiterate that the frequent dosing of BCMA bispecifics does increase infection risk and can place a significant burden on patients due to initial hospitalization and ongoing treatment schedules until progression.[24,29,30,37,38]

Dr. Turck:
Thank you, Dr. Banerjee. Now I'd like to dive deeper into the challenges surrounding treatment administration. Starting with CAR T-cell therapy, could you elaborate on the barriers associated with this approach and how they impact your patients with multiple myeloma?

Dr. Banerjee:
Of course. One of the barriers is the geographic distribution of CAR T centers, which are predominantly located in urban areas, like here in Seattle.[39,40] This limits patient access to these advanced immunotherapies in smaller practice setting, which often treat a more diverse patient population with varying socioeconomic statuses.[1,36,39–41]

Even if one assumes access to CAR T therapy, the logistics of CAR T therapy can also be very complicated. As I touched upon earlier, patients typically need daily monitoring for adverse reactions for 7 to 10 days following CAR T infusion, which again does require an inpatient stay at some institutions. The FDA requires that patients must also remain within the vicinity of their care center for about 4 weeks following CAR T therapy as well.[1,27,31,36] Finally, autologous CAR T is a complex drug that's essentially hand-made for each patient.[36] Practically speaking, vein-to-vein times with CAR T therapy are typically about 8 to 10 weeks.[34] That's the time between a patient's blood collection for CAR T manufacturing to when the patient receives a CAR T infusion after lymphodepleting therapy.[35]

With autologous CAR T therapy, there's also the possibility of manufacturing an out-of-specification product. That refers to a product that's expected to be clinically effective, but that doesn't fully meet the FDA specified release criteria for commercial products. These situations can further complicate treatment logistics and delay treatment.[1,36]

All in all, I think it's fair to say that CAR T therapy poses significant logistical hurdles for patients. Even highly motivated patients and caregivers must be prepared to relocate twice if they don't live close by to a CAR T center: once for approximately two weeks for T-cell collection process, and then again for roughly 5 to 6 weeks for the actual CAR T infusion itself and monitoring.[27,31]

One study estimated that approximately half of patients who may be candidates for CAR T therapy aren't able to actually receive it. Given how often we recommend CAR T therapy for patients in the relapsed and refractory setting, navigating these complex logistics remains one of the biggest problems we encounter in providing care for our patients.[1,36]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Rahul Banerjee to discuss the latest advancements and ongoing challenges in the treatment of relapsed and refractory multiple myeloma.

Now, Dr. Banerjee, if we switch gears and focus on BCMA bispecifics, what barriers might patients and clinicians encounter?

Dr. Banerjee:
That's a great question. Thanks, Dr. Turck. Before I dive into it I think it's worth noting that, generally speaking, T-cell-redirecting bispecific antibodies exist for other disease states as well.[42–44] So, these therapies are likely to become increasingly available in cancer centers across the US—not just for myeloma. In 2020, the Association of Cancer Care Centers surveyed community clinicians who cared for patients treated with bispecific antibodies, focusing on the challenges associated with such treatments.[37] While these are older data, 59 percent of the surveyed clinicians encountered barriers to bispecific antibodies. These included provider and patient hesitancy, as well as logistical challenges, for example, the lack of in-house expertise or to effectively manage remote-area patients and their side effects.[37]

Additionally, the FDA-mandated Risk Evaluation and Mitigation Strategy, or REMS program, is a drug safety program that's designed to manage the risks associated with certain medications. While the REMS program provides important safeguards, its administrative burdens and certification requirements can be challenging, particularly for community oncologists who may only encounter a couple of patients per year who require BCMA bispecifics.[45]

From my perspective, another barrier is the logistics of initiating BCMA bispecific therapy, particularly during the step-up phase, where the risk of CRS is quite high. Currently, some treatment centers, even in the academic setting, continue to perform inpatient step-up dosing due to required monitoring for adverse events, while other centers may hesitate to implement bispecifics entirely because of the

CRS risk.[37]

Establishing outpatient step-up dosing may seem like the solution, but that can also be challenging because of the required staffing infrastructure and call schedules, which leads to a reliance, historically, on hospitalizations for this process. However, many community oncology practices are contracted by hospitals rather than being hospital owned. As a result, these practices may have difficulty getting hospitals to cover the cost of inpatient bispecific dosing.

But even with these challenges, I hope that one day, with further advances in research and innovation, all patients with multiple myeloma who need BCMA bispecifics will have access to outpatient bispecific initiation close to where they live.

Dr. Turck:
I see. So given the challenges faced by patients who aren't receiving these novel immunotherapies, what are the key takeaways for addressing their needs and improving their outcomes?

Dr. Banerjee:
Absolutely. Historically, patients with relapsed and refractory multiple myeloma who are triple-class-exposed have demonstrated inferior outcomes with standard treatment options compared to patients who are not triple-class exposed.[11,12,28]

And although recently approved BCMA-targeted, T-cell redirecting therapies, for example, CAR T and bispecifics, have shown improved efficacy for these patients, many still face challenges due to prolonged times-to-treatment, intolerability, and inaccessibility.[1,18,27,28,31,36,40,46]

So while the era of BCMA bispecifics is undoubtedly here, I think it's important that we try to further advance the research investigating immunotherapies, particularly around improving CRS and mitigating infection risks.[37]

In order to achieve this goal in the future and ensure equitable access across the US, we also have to address these logistical barriers, including having a BCMA immunotherapy option that can be safely administered in the outpatient setting without requiring hospitalization.[37] By doing so, we can broaden the reach of these novel immunotherapies and improve care for all patients with relapsed and refractory multiple myeloma.

Dr. Turck:
Those are great insights for us to think about as we come to the end of today's program. And I want to thank my guest, Dr. Rahul Banerjee, for helping us better understand the needs of patients with relapsed and refractory multiple myeloma and how future investigations can help. Dr. Banerjee, it was wonderful speaking with you today.

Dr. Banerjee:
Likewise. Thanks, Dr. Turck. These conversations are important, and I'm glad I was able to share some insights.

Announcer:
This program was sponsored by AbbVie Oncology US Medical Affairs. If you missed any part of this discussion, visit Industry Features on ReachMD dot com, where you can Be Part of the Knowledge.

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