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BCMA CAR-T in Multiple Myeloma: Current Practice and What's Next

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Audience questions and answers

Dr. Portuguese answered many questions for us both after the presentation and via follow-up email. The questions have been grouped by topic for easier reading.

Timing of CAR-T in the Disease Course

Q. If a lower disease burden leads to better outcomes, is there research planned to give CAR-T earlier, before relapse, including in patients already in remission after first-line treatment?

A. Yes. We have participated in studies moving CAR-T into earlier lines of therapy, including CARTITUDE-6, which compares standard treatment incorporating autologous stem cell transplantation with cilta-cel-based therapy. The study is no longer enrolling, but patients continue to be treated and followed, along with the DURGA 5 and DURGA 6 trials.

We give transplant in the upfront setting because the deepest response most patients get from conventional, non-immunotherapy regimens is usually their first response: we give four cycles of Dara-VRd, achieve that first deep response, then deliver transplant. So that may be the optimal time to give CAR-T as well. CAR-T is more permissive of disease status than transplant is. With transplant, if someone does not have fairly good disease control, it is almost not worth doing: the benefit is greater with a very good partial response, an M-spike under 0.5, free light chains under 10, bone marrow plasma cells under 5 percent. With CAR-T, even 30 percent plasma cells in the bone marrow still responds exceptionally well. That said, I think optimizing disease status is probably good for CAR-T generally too.

More broadly, there is significant interest in moving CAR-T earlier in the disease course, including before traditional biochemical relapse. The hope is that treating patients earlier, when disease burden is lower and T cells may be healthier, could improve long-term outcomes and increase the likelihood of durable remission. We may be opening two additional studies in this space in the near future, which reflects how much momentum there is behind this idea.

With CARTITUDE-1, we are starting to wonder whether some of the patients five years out are cured. Time will tell, but some people are starting to think along those lines. If we are going to shift from a control mindset to a cure mindset, I think we have to move this to the front line, where we can get the best response going in. We also know the disease can clonally evolve and develop resistant subsets, so the most opportune time is probably earlier in the disease course.

Bridging Therapy

Q. I was the last patient enrolled in the AZD0120 trial at Swedish. My leukapheresis was July 13, and my CAR-T infusion is scheduled for August 18. I'm not being given any bridging therapy before then, and I'm wondering if that's expected.

A. That is a huge barrier. Because product turnaround on these trials is faster, that limits the ability to bridge in the first place. Phase one and two trials generally require patients to maintain a certain amount of measurable disease, often an M-spike over 1 gram per deciliter or free light chains over 10 milligrams per deciliter, at the time of infusion, so treating someone right before rechecking those numbers risks dropping them below the threshold and out of the trial. Turnaround on the faster trials is typically about two weeks, and washout requirements limit bridging to maybe a three-day window if we use it at all, and there is usually not enough benefit from one dose of bridging to justify that risk. So on most of these trials, we do not bridge. The good news is that with both the AstraZeneca product and anito-cel, the risk of Parkinsonism, Bell's palsy, and colitis is, as far as we know, close to zero, so the need to have disease under exquisite control before infusion is not as important as it is with Carvykti.

Q. Are CELMoDs useful as bridging therapy?

A. Potentially, yes. CELMoDs are not yet FDA-approved. The PDUFA date for iberdomide is August 17, 2026. [Editor's note: Iberdomide received FDA approval on August 13, 2026.] In general, any effective therapy can potentially be used as bridging treatment while patients are waiting for CAR-T manufacturing. If a patient's disease is sensitive to a CELMoD, it could certainly be a reasonable bridging option in some situations.

Caregiver Support

Q. My biggest challenge is caregiving. I don't have family or close friends nearby who can help, only a part-time caregiver whose arrangement doesn't really cover what CAR-T requires, and paying him beyond his contracted hours isn't something I know how to manage. This seems like a big gap, especially since a lot of patients are older and don't have surviving family to lean on. I'm also wondering if the group has ever thought about coordinating support among patients going through CAR-T at the same time.

A. It is genuinely difficult. You try to cobble together a plan with what you have and get as much support as you can. Not everyone has a perfect 24/7 caregiver plan, and usually that is fine, but it is suboptimal and it does put you at some risk, especially if neurotoxicity develops and you need someone to notice and say something. Having a caregiver for at least the first two weeks after CAR-T is most critical. What is acceptable to your specific immunotherapy team is a negotiation and depends on a lot of factors. On coordinating shared support among patients going through CAR-T at the same time: that is a good idea, and it has not really been explored to my knowledge.

Stem Cell Banking

Q. I have stem cells banked. Should I keep paying to store them?

A. My political answer is to discuss it with your oncologist, but if I were a myeloma patient, I would bank them if I could afford it, as a bottom line. It is an insurance policy: hopefully you never need them and end up thinking you wasted a few thousand dollars. But if you develop persistently low blood counts after CAR-T cell therapy, giving back one to two million of your own frozen stem cells, no chemo, just thawing and infusing them, can fix the problem in almost 100 percent of patients who need it. Most people never get to that point, but for the few who do, it is an exceptionally effective rescue.

Q. I never had a stem cell transplant. I was stage one at diagnosis under Durie-Salmon staging, so I wouldn't have been covered by Medicare for it. Right now my free light chains are good, but I'm not MRD negative, and I don't have any stem cells stored to use as a rescue option. I'm 77, and I think I'm getting close to the point where harvesting wouldn't be an option anymore. I have standard-risk disease, a gain of 1q. Should I go ahead and get stem cells harvested and stored, just to have as insurance for CAR-T down the road?

A. That's a good question, and it's hard to answer. Conventionally we haven't really offered stem cell harvesting specifically to have in reserve for CAR-T. I don't think anyone really knows the right answer here. Needing them is pretty uncommon: we've only done a handful of stem cell boosts at our center, though some places do more, up to 8 or 10 percent of CAR-T patients at some centers. I'm not sure it's worth the hassle in general, but it's such a personal decision, since

there isn't a clearly right or wrong answer, that it really depends. Some people have specific risk factors for worse blood count recovery after CAR-T, like bone marrow fibrosis or clonal hematopoiesis; if there's a specific reason to think your risk is elevated, it may be reasonable to consider it. Without a specific reason, it's harder to make the case that it's necessary. It's much more likely than not that you wouldn't actually need stored cells if you went through CAR-T. Ultimately it comes down to personal risk tolerance and age: we don't have a hard upper limit for CAR-T, but 80 or so is roughly the ceiling. So it also depends on your risk of relapse; if that risk is thought to be low, you might not end up being a CAR-T candidate at all, and storing cells wouldn't be worth it for that reason.

Toxicity and Safety

Q. I'm concerned about the effects of wiping out the B-cell lineage with CAR-T. Do you worry about loss of immune memory or the ability to respond to vaccines? Does that risk increase if a therapy targets something like CD19 earlier in B-cell development, so that people become aplastic for B cells and dependent on immunoglobulin infusions for life?

A. That's a really good question. Many patients become hypogammaglobulinemic after CAR-T, including BCMA-targeted CAR-T, and we recommend monthly IVIG infusions until it resolves; some patients need it for six months, some do not need it at all. There is some loss of immune memory, and we generally recommend revaccinating, similar to after a stem cell transplant, though it's a different process. With a stem cell transplant, think of your immune system as an office building: we fire all the workers and shred their files, then even once we rehire everyone, they're untrained with no procedures in place. It's a very different, much less severe version of that with CAR-T, an order of magnitude less impactful to your immune system than a transplant, but still real. We generally recommend revaccinating at six months, though you can get the COVID vaccine at three months. It's not that your entire immune memory is wiped away, but probably a significant fraction of it is. Whether dual targeting BCMA and CD19 makes this worse, I don't think we really know yet. I would imagine the answer is yes, but we'll have to see what the actual magnitude is.

Q. Is it true that you can't drive during CAR-T recovery?

A. There used to be a REMS risk mitigation program with CAR-T that forbid driving for eight weeks, but that was abolished in the past year; it was felt to be unnecessary. That said, it's probably not a good idea to drive within the first four weeks. What we don't want is someone developing cytokine release syndrome or neurotoxicity while behind the wheel, which would be genuinely dangerous. The first two weeks are the mission-critical window; after that, the risk of an incident is pretty low. In general we don't want you driving for the first four weeks, but it can be a discussion with your team about your specific risk of ICANS. By 21 days, that risk is close to zero.

Q. Is CAR-T all done outpatient? And what does recovery actually feel like: are you mostly resting at home, or do people feel okay?

A. It's given outpatient, but if you develop cytokine release syndrome, neurotoxicity, or a fever, you're admitted. Our inpatient team is an immunotherapy team, an extension of the outpatient program, so there's close coordination rather than handing you off to a random team. Most people feel reasonably good. The lymphodepleting chemo can cause some nausea, diarrhea, and fatigue, but most people feel okay, and unlike with a stem cell transplant, where nearly everyone feels crummy, some people get through CAR-T without ever feeling that bad. Most feel nearly back to normal by the end of the first month and fully back to normal at two to three months; with a transplant, that timeline is closer to two to three months for nearly normal and four to six months for fully normal. If someone develops significant cytokine release syndrome or neurotoxicity, recovery takes longer, but the typical experience is a few days in the hospital with grade one symptoms, then outpatient and nearly back to normal within a month. I think most people are surprised there aren't more side effects than there are.

Q. If a patient wants to be in the hospital for closer monitoring during CAR-T, is that an option?

A. It really depends. We don't want to admit someone just because they want to be there. We try to be good stewards of hospital resources, and often nothing happens in the first seven days: you get the infusion, then you wait. When Carvykti first came out, we admitted everyone for that first week, and people hated it: they were bored and didn't like the food, and wanted to leave. We've moved away from that, and our goal now is to keep people outpatient as much as possible. You really don't want to be in the hospital if you don't need to be: they wake you every four hours, the food isn't great, and you're confined to a unit, walking in circles all day.

Q. I've been having headaches for about two weeks, every day, along with a low-grade fever. I have a history of cryptococcal meningitis from about four years ago, and my care team has had me on preventive treatment for it since. My CAR-T was about three months ago, and my immune system and blood counts have stayed very low, so I've needed frequent blood transfusions. I'm wondering if the meningitis could come back because of how low my immune system is, how I would even get infected again, whether it's more about my environment or my immune system, and how I can avoid it. I wear a mask everywhere I go and don't understand how this could be happening. Is it common to have headaches like this three months out from CAR-T?

A. That's a fairly complicated situation, and I'm sorry you're dealing with these consequences of CAR-T. Headaches at three months out are not common; that would not be typical. On cryptococcus: it can be regional, so if you're immunosuppressed and in certain parts of the world, you're at higher risk. It can involve the lungs or, in the most concerning cases, the central nervous system; if you were cleared to proceed to CAR-T, that likely included a brain MRI and a lumbar puncture to rule out CNS involvement beforehand. For patients who test positive for cryptococcal antigen, the typical approach is a month of fluconazole before proceeding,

assuming there's no CNS involvement, then fluconazole for several months afterward as prophylaxis to reduce the risk of flare-up. These are specialized situations that need close collaboration between infectious disease, the immunotherapy team, and the myeloma team, so I don't want to overstep with specific advice without knowing the full case. It also sounds like there are issues with delayed count recovery, which is unusual this far out and worth a direct conversation with your oncologist and infectious disease team. It is definitely not typical.

Q. My ejection fraction dropped from 60 percent to 54 percent. I had severe orthostatic symptoms starting with induction and continuing through my transplant that took several years to fully resolve. My doctor has told me CAR-T would be my next option if I relapse, and honestly, after how hard transplant was, I'm terrified of going through something like that again. How does CAR-T compare from a cardiac standpoint?

A. An ejection fraction of 50 to 54 percent would be absolutely no problem for CAR-T eligibility. I don't have a crystal ball, and I can't say you'd have no problems at all if you went through it, but in general, cardiac toxicities are much less common with CAR-T than with transplant. A lot of patients who had a rough time with transplant find CAR-T comparatively easy. Rare cardiac toxicities do happen with CAR-T, and if it happens to you, a statistic doesn't matter, it's a real problem, so it's hard to answer with certainty. But from a cardiac perspective, CAR-T is a lot safer: orthostatic hypotension can occur, but it's less common than with transplant, and the mechanism is completely different. Transplant uses the maximum dose of chemotherapy a person can tolerate; CAR-T harnesses your immune system instead. It's unlikely you'd experience anything in the same range as what you went through with transplant. If you do move toward CAR-T in the future, I'd want to bring in our cardio-oncology team for a workup to better estimate your risk. Overall, though, the risk is much, much lower with CAR-T than with transplant, and I'd encourage you to keep an open mind about it.

Q. What has the rate of enterocolitis been among Hutch CAR-T patients?

A. To date, we have seen one case of IEC-associated enterocolitis in a patient treated with Carvykti. That said, this is an uncommon but likely underrecognized complication. The best current estimate is that the true incidence is probably around 2 to 3 percent, although this remains an area of active investigation.

Q. Are high-risk genetics a risk factor for ICANS or enterocolitis?

A. Based on what we know today, high-risk cytogenetics do not appear to increase the risk of acute CAR-T toxicities such as ICANS or IEC-associated enterocolitis. High-risk cytogenetics remain very important from a disease biology and relapse perspective, but they do not appear to meaningfully influence the risk of these specific toxicities.

Eligibility and Prior Treatment

Q. Is there any prior treatment that would take a patient out of the running for CAR-T?

A. In the absolute sense, no, though getting insurance coverage for a second CAR-T can be a logistical challenge. If you've recently been on a bispecific antibody like talquetamab, we'd want a washout of ideally several months before CAR-T, because recent bispecific exposure seriously raises the risk of manufacturing failure: at our center, we had five patients who received a bispecific right before leukapheresis, and two of the five had a serious manufacturing problem, one failed to manufacture entirely and one came out of specification. That risk became so widely recognized so quickly that it's actually underrepresented in the published literature. Going straight from an intensive salvage chemotherapy regimen into CAR-T can also hurt manufacturing, so patients usually need some recovery time first. The other factor is resistance: if someone had a long, good response to a BCMA-targeted therapy like teclistamab that eventually stopped working, they may not respond as well to BCMA CAR-T, particularly within about nine to twelve months of that bispecific. There is some data suggesting CAR-T given within nine months of a BCMA bispecific doesn't work as well. Otherwise, there isn't really another prior treatment that meaningfully affects eligibility or outcomes.

Monitoring and Disease Tracking

Q. What tracking or follow-up is being done on CAR-T patients? CAR-T is so new: what data are we gathering about the long haul?

A. We now have five-year follow-up from CARTITUDE-1, which still isn't truly long-term. We run two programs to follow patients over time. One is a long-term follow-up program, mandated by the FDA for any center offering CAR-T, that can track patients for up to fifteen years through a research consent, periodic surveys, and records from your oncology team, looking beyond just response numbers at functional status: whether you're living a normal life, not just what your M-spike or free light chain lab shows. The other is a CAR-T biorepository, led by Jordan Gauthier, one of our immunotherapy attendings, with me as a sub-investigator. Because you can't go back in time to collect samples once someone has a late side effect, we try to collect bone marrow and blood samples across the board: before and after CAR-T, then blood draws on a set schedule through day 30, so that if something unexpected happens, or if we want to compare patients with better versus worse responses, we have the samples to look at.

Q. When you're measuring MRD negativity, are you using ClonoSEQ or looking at M-spikes?

A. ClonoSEQ, which is currently the most sensitive test for measurable residual disease, run in the bone marrow, since that's where myeloma actually lives; testing it in the blood is essentially meaningless, though I've seen some community doctors do that. It can detect one myeloma cell

among a million normal cells by tracking the genetic fingerprint of your specific myeloma, which requires a sample from an earlier bone marrow biopsy to identify that clonal signature in the first place. Most people who go through CAR-T become MRD negative

Outcomes

Q. Is there a rule of thumb for how long CAR-T is expected to work?

A. The boilerplate answer is a median duration of response of about three years with Carvykti. Standard-risk patients, about 80 percent of myeloma patients, tend to do a bit better than that; high-risk patients, the other 20 percent, tend to do a bit worse. True extramedullary disease, plasmacytoma not connected to bone, or plasma cell leukemia, more than 5 percent circulating plasma cells, both make CAR-T less effective. For standard-risk disease, I'd counsel someone to expect at least three years; I can't predict exactly when someone will relapse, but in aggregate that's my expectation. For high-risk disease, I'd say I'll be happy with more than two years. For extramedullary disease, it's probably on the order of a year and a half to two years.

Q. If CAR-T fails, what's next: a bispecific?

A. That's really the million-dollar question, and it's genuinely tough, to be honest and frank with you. We're now entering a phase with more patients relapsing after CAR-T, and managing their care is challenging. It depends heavily on what they've been exposed to and what they're resistant to. Targeting something different, like GPRC5D with talquetamab, is a common strategy. We can use BCMA bispecifics too, but a BCMA bispecific after BCMA CAR-T usually doesn't work that well; some patients get a partial response, but it's typically not durable. We're working with Fred Hutch pathology and UW flow cytometry to better quantify how much BCMA is still present on plasma cells, which could help guide treatment: patients with more BCMA still expressed might benefit more from targeting it again. We're also looking at moving beyond FISH toward whole-genome platforms like PlasmaSeq or GenoPredicta in the bone marrow, which can show not just the classic translocations FISH catches but also mutations or deletions in genes like CD38, BCMA, or GPRC5D. Combining pathology immunostains with genomic assays could help guide treatment so we're not wasting a line of therapy on a target that isn't there. This is becoming a bigger problem as more patients move into the post-BCMA-treatment phase of care.

Drug Pipeline

Q. How far away is anito-cel from approval?

A. The current FDA target action date, the PDUFA date, for anitocabtagene autoleucel, anito-cel, is December 23, 2026. If approved, it could become available shortly thereafter.