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Identifying Candidates for CAR T-Cell Therapy in Relapsed/Refractory ALL

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Kite Pharma. Here's your host, Ms. Ashley Baker.

Ms. Baker:
This is *Project Oncology* on ReachMD, and I am nurse practitioner Ashley Baker. Joining me to talk about how we can identify candidates for CAR T-cell therapy in acute lymphocytic leukemia, or ALL for short, is Dr. Chenyu Lin. Dr. Lin is an Assistant Professor of Medicine at Duke University School of Medicine in Durham, North Carolina. Dr. Lin, thanks for being here today.

Dr. Lin:
Thanks for having me. I'm excited to be here to talk about CAR T in ALL.

Ms. Baker:
So if we start with some background, Dr. Lin, how is CAR T-cell therapy used to treat patients with relapsed/refractory ALL? And what kind of impact can this approach have?

Dr. Lin:
Yeah, so CAR T is interesting. It's a cellular therapy in that it uses the patient's own T cells, which are part of their immune system. These T cells are collected from the patient through a process called apheresis, and then those are shipped to a manufacturing facility where they're expanded and engineered to express a chimeric antigen receptor, and that's the CAR part of CAR T. So these receptors target a specific protein on the leukemia cell surface, in this case CD19. So these CAR T cells are essentially super energized, targeted killing machines against cells that express CD19, which includes ALL cells.

So the reason I say all this is because CAR T offers a different mechanism of killing cancer cells compared to cytotoxic chemotherapy or some of our more traditional immunotherapies that we're used to seeing. And what this means is that it's often able to get around the resistance that cancer cells develop against our standard treatment options.

I will highlight that in contrast to transplant, we don't think of CAR T as being as intensive or as morbid, so more patients can qualify for CAR T and more can tolerate CAR T. So when you ask about impact, I think that's a real impact to have an effective treatment for relapsed/refractory B-cell ALL that has a potential for cure but with fewer side effects and more accessibility to our patients.

Ms. Baker:
And when should we consider CAR T-cell therapy in a patient's treatment journey?

Dr. Lin:
Yeah, that's a great question. This is part of an evolving discussion in our field on how to sequence therapies for ALL. There's some controversy, a lot of debate, and there really isn't a one-size-fits-all answer; it really depends on the patient. So CAR T is approved by the FDA for relapsed or refractory B-cell ALL, so we would consider it on label when we need a later line of therapy after the leukemia has come back or if it doesn't respond to the initial chemoimmunotherapy regimen.

The first thing to remember is that we only consider CAR T for B-cell ALL because our current CAR T options all target CD19, which is an antigen in the B-cell lineage. In contrast, T-cell ALL, unfortunately, does not currently have an approved CAR T product. There's very active research in this area to try to develop novel CAR T products against T-cell antigens, and I'm hoping we'll hear more about those in the coming years. But for B-cell ALL, when we think about the patient's journey and how they progress, many of our patients can have their leukemia be effectively controlled with just our current arsenal of first-line chemotherapies and immunotherapies.

If the patient's leukemia doesn't respond to frontline treatment or if the disease comes back, then we get more worried because perhaps then their disease is resistant, and more chemo may not benefit them, and it's not likely to get a cure. So at that point, we're in the relapsed or refractory setting. And for most oncologists, if you haven't used it yet, then you're thinking about certain immunotherapies like blinatumomab, which is a CD19/CD3 bispecific engager, or inotuzumab ozogamicin, which is a CD22-directed antibody drug conjugate. So these are all valid options in the relapsed setting. But we should remember that in frank relapse of ALL, these don't tend to lead to durable remissions, so more often they're used as a lead-in or a bridge to a more definitive therapy.

So what are these definitive therapies? Well, in patients with relapsed disease, if we're aiming for durable remission and hopefully a cure, we start thinking about cellular therapies. And that includes the traditional gold-standard treatment for relapsed ALL, which is an allogeneic stem cell transplant and also CAR T-cell therapy. So those are the two primary cell therapy modalities. How we pick between the two—how do we identify who should get transplant and who should get CAR T—that's a fairly nuanced discussion and really depends on the individual characteristics of the patient, characteristics of the leukemia, and also the logistical considerations that play a large role in whether cell therapies can be given.

Ms. Baker:
With all that in mind, let's zero in on some patient identification strategies. First, what clinical characteristics do you consider?

Dr. Lin:
So when I think about how to identify a good candidate for CAR T, I really use some of the same risk-benefit considerations that oncologists use every day for chemo. So one, is the patient going to respond or benefit from the treatment? And two, are they going to tolerate the treatment? In terms of tolerability, just like with chemo, fitness does play a role in the eligibility for CAR T. You want a reasonable performance status since CAR T side effects can be pretty intense. Age is not an absolute contraindication to CAR T; in some cases, older patients may actually respond better to CAR T.

We should also keep in mind some of the unique side effects of CAR T, which are cytokine release syndrome, neurotoxicity, and prolonged cytopenias. So comorbidities really have to be considered in the context of these toxicities.

There are certain characteristics of the leukemia that make it less likely to respond to CAR T. So if the patient has gotten prior treatment with blinatumomab, which is that CD19 bispecific, the leukemia might lose the CD19 expression, which means that the CAR T won't have an antigen to target anymore. If possible, I personally do check for CD19 expression at the time of relapse when I'm considering CAR T just to reassess eligibility and make sure that the patient is likely to benefit. And then there are some other poor prognostic factors; high tumor burden and presence of extramedullary disease are associated with worse outcomes from CAR T as well.

Ms. Baker:
And are there any other factors you keep in mind when determining a patient's eligibility for CAR T-cell therapy?

Dr. Lin:
Yeah, so we talked about some of the clinical factors that impact CAR T eligibility, but there are a lot of logistical considerations as well, and I think often these tend to impact our patient's ability to get CAR T more than even the clinical factors do, which is unfortunate.

So first of all, with our current technology and with our healthcare system, they don't allow for rapid delivery of CAR T; you can't just prescribe it and grab it off the shelf. So first, you need insurance approval. It's an expensive drug, and not all insurance will reimburse fully for CAR T, so you have to find a center that will take your insurance. Oftentimes, even when it's submitted, there are delays and then appeals that are required.

Once insurance is approved, from the time of the apheresis to the infusion of the CAR T cells, which is what we call vein-to-vein time, that can still take several weeks. So the entire process could be a month or more. The other major issue is just the logistical complexity that surrounds CAR T. So CAR T is a complicated process, and it can have significant side effects. So patients do have to travel to a CAR T center, and they require close monitoring for about a month or so. Many community hospitals don't give CAR T, and they're not equipped to treat CAR T toxicities. So most CAR T centers that I'm aware of currently require that patients stay within a certain driving distance, about 30 to 60 minutes typically from their center, and they have to stay there for about a month. It's also required they find a 24-hour caregiver, which usually that's a family member or a friend, and that person then has to take time off work to take care of the patient and monitor them for side effects. So knowing all this, these can be considerable burdens for our patients, especially those patients with fewer socioeconomic resources.

Ms. Baker:
For those just joining us, this is *Project Oncology* on ReachMD. I'm nurse practitioner Ashley Baker, and I'm speaking with Dr. Chenyu Lin about patient identification strategies for CAR T-cell therapy in acute lymphocytic leukemia.

So, Dr. Lin, once you identify an appropriate candidate, what are some best practices for referring them?

Dr. Lin:
So I usually tell my partners that when in doubt, it would be better to just refer the patient for consideration of CAR T, even if there are only trace amounts of measurable residual disease. If you don't believe that the remaining available therapies are likely to lead to long-term remission, then it's right to refer early to a CAR T and transplant center so they can be evaluated. And preferably that referral will happen before the second- or third-line of therapy and preferably not later than that.

If you practice in the community and you know an academic leukemia specialist, then pick up the phone and call them to discuss the patient. If you don't have a direct line to a specialist, then it's reasonable to send a referral to the academic center and ask to speak with a leukemia physician or ask that the referral be expedited because it's a relapsed acute leukemia. I think most centers will understand the urgency and try their best to connect the patient quickly. So we always prefer that the patient be referred sooner and in earlier lines of therapy so that there's enough room to salvage and get them to CAR T if possible.

Ms. Baker:
Well, you've certainly given us a lot to think about. But before we close, Dr. Lin, do you have any final thoughts on how we can better identify candidates for CAR T-cell therapy?

Dr. Lin:
Yeah, I think from everything we talked about, the key takeaways are to refer early if you can and to refer even if you're not sure that they'd be a candidate. Some of the traditional barriers to an allogeneic stem cell transplant—factors like older age, performance status, comorbidities, and disease status—we really try to work around some of this for CAR T if we can because we know that it's not as intensive as an allotransplant. And some of these other financial barriers to transplant—like housing, travel, and food—a lot of this could be offset by the CAR T company, which typically isn't available for transplant. So we talked a lot about how to identify patients for CAR T today, but at the end of the day, we understand that for many of these patients, there just aren't a lot of options left. So we would consider CAR T as long as we believe that ultimately there's more benefit than harm for the patient.

Ms. Baker:
With those final thoughts in mind, I want to thank my guest, Dr. Chenyu Lin, for joining me to share strategies for identifying appropriate patients with acute lymphocytic leukemia for CAR T-cell therapy. Dr. Lin, it was great having you on the program.

Dr. Lin:
Thanks for having me.

Announcer:
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